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MATHEMATICAL MODELS OF CHEMOTHERAPY AND IMMUNOTHERAPY

by

FRANK NANI

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree DOCTOR OF PHILOSOPHY

in

APPLIED MATHEMATICS

Department of Mathematical Sciences

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ABSTRACT

Generalized deterministic, mathematical models depicting the dynamics of cancer and normal cells under chemotherapy and adoptive cancer (cellular) immunotherapy (ACI) are formulated and analyzed using the techniques of linearized stability, persistence theory, Floquet theory, Liapunov stability, Hopf-Andronov-Poincaré bifurcations and implicit function theory. The models incorporate most of the physiological features of tumor-normal cell interactions such as competition, existence of threshold carrying capacities, and therapy induced destruction of normal and cancer cells. Specific numerical examples are given to illustrate the associated therapy-induced dynamics.

Explicit mathematical criteria are formulated for persistence of disease, local and global existence of clinically preferred tumor-extinction rest points or periodic orbits, as well as the associated criteria for therapeutic failure for piece-wise continuous (periodic) and constant drug administration.

Numerical examples and computer simulations and the associated graphs are exhibited for various clinically plausible parametric configurations.

The results and theorems involving the models are much more general and in most cases represents new results in mathematical modelling of cancer chemotherapy and immunotherapy. The numerical simulation results illustrate the clinically observed therapeutic profiles in chemotherapy and immunotherapy. The theorems present some attempt to find quantitative criteria for success and failure of therapy and could be utilized by clinical oncologists.

DEDICATION

This thesis is dedicated to the memory of the following deceased friends and scholars:

Dickson 'Kosoko' Tsivor

Prosper Ofosu

Harry Danku

Raymond Attor

Rudolph Nani

whose inspirational conversation and academic companionships are greatly missed.

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CHAPTER 1

INTRODUCTION

1.1. Mathematical Modelling and Pathological Processes

Bio-medically, a person can be defined as a cellular configuration of matter, endowed with a unique morphologic, pathologic, genetic and physiologic parametric configuration. This dynamic parametric configuration characterizes the state of health and well being of a person. There exist in the human physiologic system certain units such as enzymes, hormones, growth factors and other regulatory mechanisms in addition to the immune system which constitute the intrinsic defense network against bacterial and viral pathogens and also against the onset of carcinogenesis [14]. Nevertheless, a person may eventually succumb to the onslaught of disease pathogens and cancer and consequently become temporarily or permanently incapacitated, due to the circumvention of the immune defense mechanisms and the body's other regulatory mechanisms.

The restoration to the disease-free state of a cancer patient can be accomplished by surgery, chemotherapy, immunotherapy, phototherapy and other treatment modalities [14]. Apart from surgery, which relies mostly on the accuracy of the x-rays and other imaging techniques, the other treatment modalities including chemotherapy and immunotherapy rely on accurate staging of the tumor, the dynamical properties of the tumor, the kinetics of tumor-host-drug interactions and the optimal administration of the anti-cancer drugs.

Clinically it is observed that every pathological process, including carcinogenesis, possesses a time evolution profile. Thus, if the kinetic parameters characterizing a pathological process such as cancer can be determined accurately, it

will be possible in principle to establish quantitative therapeutic criteria depicting the prognosis or outcome of therapy. Since therapy may perturb and alter the initial pathological parametric configuration of the cancer cells, it may be prudent to use mathematical modelling and analysis to provide (i) a more rational basis for the design and optimal administration of the anti-cancer drugs; and (ii) make quantitative predictions as regards the dynamic evolution of the disease, the domain of therapeutic efficacy of the drug; and (iii) determine the general prognosis of the cancer based on the initial data and the clinical (pathological) parametric configuration of the cancer patient and the pharmacodynamics of the anti-cancer drug. In particular, the knowledge of the cancer *persistence* criteria and other evolutionary parameters and periodic fluctuations in the therapy-induced cancer dynamics will enable the medical oncologist to make rational decisions as regards the choice and implementation of drug therapy based on the mathematical relation between the dynamical variables involved in the progression of disease.

The advent of state-of-art experimental equipment and the desire to obtain quantitative therapeutic criteria have made mathematical modelling an important part of clinical cancer research. But the extreme complexity of physiological and pathological processes and the lack of reliable kinetic stoichiometry at the cellular levels compel most mathematical modellers to construct phenomenological models. These type of models possess a degree of realism which is subject to contemporary clinical data and knowledge and provide qualitative results and predictions. The use of computer simulations is now an accepted and important tool in the modelling of bio-medical systems including cancer dynamics. The simulations allow both the mathematicians and the medical oncologist to observe model behavior graphically and under a range of 'user-friendly' conditions. Mathematical models could be deterministic or stochastic. Basically, the two approaches describe the

same basic dynamics. Stochastic modelling is used if there is randomness or uncertainty about the evolutionary process. But if there is abundance of experimental kinetic data and established physiological pathways and mechanisms on a given pathological process, it is possible to use deterministic modelling techniques. A non-stochastic model may be more tractable and much easier to simulate under various parametric configurations as compared to their stochastic analogs. The output from a deterministic model can be predicted completely if the input parameters and the initial states of the model are known. But a stochastic model in a given initial state will respond to a given input parametric configuration by producing a range or a distribution of output variables. Many repetitions are required to determine the stochastic output adequately. In this thesis, deterministic modelling will be used to describe cancer chemotherapy and immunotherapy. However, stochastic modelling may be more effective in certain areas of cancer research such as the process of carcinogenesis and cancer drug resistance [22,28,44], as well as cancer cell proliferation [13].

1.2. Cancer: Carcinogenesis, Chemotherapy and Immunotherapy

Cancer is a malignant disease in which certain cells originating from various anatomic regions, proliferate in disregard to the growth regulatory mechanisms of the body. The cancerous cells biotransform to stages of greater malignancy, characterized by oncogene activation/mutation, heterogeneity, invasiveness and metastasis [14].

Carcinogenesis is a multistage process: (i) initiation, (ii) promotion, (iii) local cancer (cancer *in situ*), (iv) invasion/angiogenesis, (v) metastasis [14]. The initiating agents consist of chemical carcinogens, viruses, radiation, ultraviolet

light exposure, DNA replication errors, stress and certain unknown factors. The application of the carcinogen (cancer-producing agent), does not lead to immediate production of a cancerous tumor. Initiation, which is the primary and essential step in the process, is very rapid, but once the initial change has taken place, the initiated cells may persist for a considerable time, perhaps even the life span of the person unless acted upon by promoting agents. The promoters include inflammation, specific promoters, hormones etc. [14]. Tumor metastasis is the major practical problem and a common cause of death due to failure of therapy. Metastasis is the process by which tumors invade the surrounding tissues. They may grow out of the organ in which they originally arise and enter into surrounding tissues.

Conceptually, cancerous tumor growth can be considered as having an avascular phase and a vascular phase. During the avascular phase, the tumor is of such a size that the surface to volume ratio of the spheroid is adequate for diffusion of nutrients and oxygen, and consequently there is rapid exponential growth. During the later stages of avascular growth, the tumor growth decelerates and at a certain critical cell number, the growth levels off into a plateau as cellular proliferation is balanced by cell death, and necrosis due to lack of oxygen and nutrients [44]. A state of dormancy occurs unless the tumor acquires new blood vessels by a process called vascularization and tumor angiogenesis.

Tumor angiogenesis enables an aggregate of tumor cells to expand beyond the maximal three dimensional size restraints imposed by space, nutrients and oxygen diffusion requirements. The primary tumor may then metastasize into other organs of the human anatomy forming secondary tumors. After neo-vascularization the primary tumor may again undergo exponential growth unless it encounters limitations. Thus realistic tumor growth may be a cascade of exponential growths

interspaced with deceleratory periods or dormant growth. However many other realistic growth scenarios are possible such as modelled by Cox et al. [22]. But generally logistic growth or Gompertz tumor growth profiles are the most frequently used models to depict tumor growth.

In general, any cellular transformation or growth characterized by invasiveness, heterogeneity, metastasis, oncogene activation, and most times greater malignancy, is called neoplasia [14]. Hence cancer is sometimes called a neoplastic disease. The term tumor which denotes swelling is commonly used to refer to a neoplasm whilst cancer is a generic term for malignant neoplasms. A malignant tumor or cancer is a configuration of neoplastic cells in an anatomic organ or tissue such that these cancer cells differ from normal cells (non-cancer cells) in histopathologic, morphologic, immunologic and cyto-kinetic characteristics.

Except for cancer of the skin which is the most common and also the most curable of human cancers, 75% of all cancers in humans in the United States occur in only 10 anatomic sites. These are the colon and rectum, breast, lung and bronchus, prostrate, uterus, lymph organs, bladder, stomach, blood and pancreas [14]. Some of the ethiologic agents according to epidemiological study are oncogenic viruses, chemical carcinogens, harmful radiation exposure and genetic predisposition [14].

In cancer treatment today, four *major* approaches can be used in efforts to obtain long-term periods of disease-free remission. These treatment types include surgery, radio therapy, chemotherapy and immunotherapy. For certain types of cancerous tumors, some form of 'cure' can be obtained through surgical debulking of the tumor followed by local radiotherapy. These combined procedures are effective unless the tumor cells are disseminated into other organs such as the lungs, central nervous system and other vital organs by metastasis. In such instances,

the only treatment modalities with potential capabilities for eradicating the micro-metastasis or secondary neoplasia are chemotherapy and immunotherapy.

Chemotherapy gained prominence in the late 1960s and 1970s due to the initial success of certain anti-cancer drugs [44,22]. But the initial optimism was abated when it was observed that therapeutic failure invariably results unless optimal drug strategies are developed. Furthermore, even with combinations of anti-cancer drugs using very efficient drug delivery systems, there exists a finite time-domain of therapeutic efficacy of the drug, after which the cancer returns causing death. However, certain cancers can still be controlled using chemotherapy under optimal drug administration, following surgery or bone marrow transplants.

There have been several mathematical models formulated to describe both stochastic and deterministic aspects of cancer chemotherapy. These include those contained in Lecture Note in Biomathematics 40, Springer-Verlag: edited by Eisen, M. Other models include those by Gatenby [21] who studied some interesting aspects of cancer and normal cells dynamics using the isocline-arrow techniques to investigate a Lotka-Volterra type model. Panetta [36], also studied pulse chemotherapy for a similar Lotka-Volterra semi-dynamical system.

Immunotherapy and gene therapy are becoming established anti-cancer treatment modalities. One of the relatively effective immunotherapeutic techniques is Adoptive Cancer (cellular) Immunotherapy. This technique is pioneered by Rosenberg and colleagues at the National Cancer Institute. Adoptive Cancer Immunotherapy (ACI) is used for particularly human solid tumors. It involves the retransfer into a patient of tumor killing lymphocytes which had been previously extracted and potentially incubated with growth factor interleukin-2. If the cancer cells in the patient are immunogenic, the ACI procedure produces clinically observable tumor remission for a finite non-zero time duration. This procedure

is extremely toxic and harmful to normal cells in the person. The therapy of a non-immunogenic tumor can be performed by tactically coating the surface of the tumor with tumor associated antigens and later targeting the tumor with monoclonal antibodies for these antigens carrying the chemotherapy or immunotherapy agent [14].

In the past, many mathematical models have been formulated to illustrate the humoral immune response involving antigens and antibodies. These include the works by Bell [5], Pimbley [38,39], Merril [34], Waltman and Butz [45], Freedman and Gatica [18]. Mathematical models describing the cellular immune response during the growth of cancer cells have also been formulated. These include models by Grossman and Berke [23], Merril [81], Albert, Freedman and Perelson [1].

1.3. Mathematical Preliminaries: Basic Definitions and Standard Theorems

In this section of the introduction we shall list all basic definitions and standard theorems which will be encountered in the forthcoming chapters.

1.3.1. Definitions of basic concepts

In this subsection we shall present the definitions of some basic concepts and parameters which will later be used in theorems or proofs of theorems in the forthcoming chapters.

D_1 : Acyclicity [cf. 10]

Consider the system

$$\dot{x} = F(x) \tag{1.1}$$
$$x(t_0) = x_0$$

where $x_0 \in \mathbb{R}^n_+$, $F : C(\mathbb{R}^n_+, \mathbb{R}^n) \to \mathbb{R}^n$, $\mathbb{R}^n_+ = \{x \in \mathbb{R}^n | x_i > 0,\ 1 \leq i \leq n\}$ and $\overline{\mathbb{R}}^n_+ = c\ell\, \mathbb{R}^n_+$ denotes the closure of $\mathbb{R}^n_+$.

Let $\mathcal{M}_1$ and $\mathcal{M}_2$ be critical points (rest points) or invariant sets on the boundary of $\mathbb{R}^n_+$, denoted by $\partial\mathbb{R}^n_+$.

Let $\mathcal{O}(x)$ denote the orbit of a point $x \in \partial\mathbb{R}^n_+$ such that

$$\alpha(x) = \mathcal{M}_1 \quad \text{and} \quad \omega(x) = \mathcal{M}_2, \tag{1.2}$$

respectively the alpha and omega limit sets of x.

Then $\mathcal{M}_1$ is said to be connected or chained to $\mathcal{M}_2$. This is depicted symbolically by

$$\mathcal{M}_1 \to \mathcal{M}_2. \tag{1.3}$$

Let S denote the set of rest points or invariant sets of (1.1) as defined by:

$$S = \{\mathcal{M}_1, \mathcal{M}_2, \ldots, \mathcal{M}_n\}. \tag{1.4}$$

If for all cyclic permutations of i and all $\mathcal{M}_i \in S$ with $i = (1, 2, 3, \ldots, n)$ we have

$$\mathcal{M}_i \to \mathcal{M}_{i+1} \to \mathcal{M}_{i+2} \to \cdots \to \mathcal{M}_n \not\to \mathcal{M}_i, \tag{1.5}$$

then the system (1.1) is said to be acyclic.

D_2 : Dissipativity [cf. 10,20]

Consider system (1.1) and let

$$x(t) = \{x_i(t)\}_{i=1}^n \tag{1.6}$$

Then the system describing the evolution of $x(t)$ is called dissipative if

$$\limsup_{t\to\infty} \|x(t)\| \leq L, \tag{1.7}$$

where L is a positive constant. In particular, the trajectories of the system are asymptotically uniformly bounded. In other words, there is a compact neighborhood

$$\mathbb{B} \subset \overline{\mathbb{R}}^n_+ \tag{1.8}$$

such that for sufficiently large $T = T(t_0, x_0)$

$$x(t) \in \mathbb{B} \quad \text{for all} \quad t \geq T \tag{1.9}$$

where $x(t)$ is any solution of (1.1) such that

$$x(t_0) = x_0 \quad \text{in} \quad \mathbb{R}^n_+. \tag{1.10}$$

For dissipative systems, the existence of an equilibrium in the interior of $\mathbb{R}^n_+$, denoted by $\text{int}\,\mathbb{R}^n_+$, is a consequence of uniform persistence [9,10].

D_3 : Hyperbolicity [cf. 9,10]

Let $E(x_0) \in \mathbb{R}^n_+$ such that $F(E(x_0)) = 0$ for system (1.1). Then $E(x_0)$ is a rest point of system (1.1).

The linearization of (1.1) in the neighborhood of $E(x_0)$ gives the equation:

$$\left.\begin{aligned} \dot{\xi} &= DF(E(x_0))\xi \\ \xi(t_0) &= \xi_0, \quad \xi \in \mathbb{R}^n_+ \end{aligned}\right\} \tag{1.11}$$

where $J_{E(x_0)} = DF(E(x_0))$ is the Jacobian matrix of the linearization (via a

Taylor series expansion around $E(x_0)$). In particular $J_{E(x_0)}$ is defined as:

$$J_{E(x_0)} = DF\big(E(x_0)\big) = \left(\begin{array}{ccc} \frac{\partial F_1(x)}{\partial x_1} & \cdots & \frac{\partial F_1(x)}{\partial x_n} \\ \vdots & & \\ \frac{\partial F_n(x)}{\partial x_1} & \cdots & \frac{\partial F_n(x)}{\partial x_n} \end{array} \right)_{x=E(x_0)}. \tag{1.12}$$

The eigenvalues of $J_{E(x_0)}$ are defined by the set

$$\sigma\big(J_{E(x_0)}\big) = \{\lambda_i | \det\big(J_{E(x_0)} - \lambda I_n\big) = 0, \quad i = 1, \ldots, n\}. \tag{1.13}$$

Respectively, the rest point $E(x_0)$ or periodic orbit $x = \psi(t)$ is called hyperbolic if the eigenvalues corresponding to $J_{E(x_0)}$ or the Floquet multipliers for $\psi(t)$ are such that they have *non-zero* real parts. Furthermore, let $\sigma\big(J_{E(x_0)}\big)$ contain n eigenvalues. Then

(i) $E(x_0)$ is a hyperbolic *saddle* orbit if there exist some $\lambda_i \in \sigma\big(J_{E(x_0)}\big)$ with $\text{Re}\ \lambda_i > 0$ and also some $\lambda_j \in \sigma\big(J_{E(x_0)}\big)$ such that $\text{Re}\ \lambda_j < 0$, for $i, j \in \{1, 2, \ldots, n\}$, but there exist no λ_k such that $\text{Re}\ \lambda_k = 0$.

(ii) $E(x_0)$ is a hyperbolic *sink* if for all $\lambda_i \in \sigma\big(J_{E(x_0)}\big)$ we have $\text{Re}\ \lambda_i < 0$, $i \in \{1, 2, \ldots, n\}$.

(iii) $E(x_0)$ is a hyperbolic source if for all $\lambda_i \in \sigma\big(J_{E(x_0)}\big)$, we have $\text{Re}\ \lambda_i > 0$, $i \in \{1, 2, \ldots, n\}$.

D_4 : Isolatedness

Theorem 1.1. *Consider system* (1.1) *and let* $F(x)$ *be analytic and let* $E_i(x_i)$ *for* $i = \{0, 1, \ldots, n\}$ *denote the rest points of* (1.1). *Then a sufficient condition for* $E_0(x_0)$ *to be isolated, is that the Jacobian matrix due to linearization of* (1.1) *in the neighborhood of* $E_0(x_0)$, *denoted by* $J_{E_0(x_0)}$, *is such that* $J_{E_0(x_0)}$ *is non-singular.*

Proof. Since $F(x)$ is analytic, we can use a Taylor series expansion in the neighborhood of $E_0(x_0)$. Thus

$$F(x) = F(E_0(x_0)) + J_{E_0(x_0)}(x - E_0(x_0)) + O(|x - E_0(x_0)|^2). \tag{1.14}$$

But $F(E_0(x_0)) = 0$ and so

$$F(x) = J_{E_0(x_0)} \cdot (x - x_0) + O(|x - E_0(x_0)|^2). \tag{1.15}$$

Any other rest point in the *neighborhood* of $E_0(x_0)$ must satisfy the relation (1.15). Since $F(E_i(x_i)) = 0$ for any other rest point as well as $E_0(x_0)$, it implies that any other rest point $E_i(x_i)$, $i \neq 0$ must satisfy the criterion.

$$J_{E_0(x_0)} \cdot (E_i(x_i) - E_0(x_0)) = 0, \quad i \neq 0. \tag{1.16}$$

But $J_{E_0(x_0)}$ is non-singular by hypothesis. Hence $E_i(x_i) = E_0(x_0)$, implying that $E_0(x_0)$ is isolated. (This condition is sufficient but not necessary.)

In the results presented in the forthcoming chapters, isolatedness (and acyclicity) will be guaranteed by the hyperbolicity and global asymptotic stability requirements for the rest points in their respective two or three dimensional subspaces.

D_5 : Persistence [cf. 9,10,16,17]

Consider system (1.1) and let

$$x(t) = \{x_i(t)\}_{i=1}^n.$$

Then x_i is said to persist if

$$x_i(t) > 0, \quad t \geq 0 \quad \text{and} \quad \liminf_{t\to\infty} x_i(t) > 0.$$

Further, the persistence is said to be uniform, if

$$\exists\, \delta > 0, \quad \ni \liminf_{t\to\infty} x_i(t) > \delta$$

independent of $x_i(0)$.

System (1.1) is said to persist (uniformly) if each component x_i, $i = \{1,\ldots,n\}$ persists (uniformly).

In particular, while persistence of (1.1) corresponds to global survival of all x_i, $i = \{1,\ldots,n\}$, non persistence corresponds to (local) extinction of at least one component.

D_6 : Liapunov functions and negative definiteness

Consider system (1.1) such that

$$F \in C(\mathbb{R}^n_+, \mathbb{R}^n), \quad x \in \mathbb{R}^n.$$

Let G be any neighborhood in $\mathbb{R}^n_+$. Then V is a Liapunov function for (1.1) on G if

(i) $V \in C^1(\mathbb{R}^n_+, \mathbb{R})$ and bounded below

(ii) $V(\bar{x}) = 0$, where $F(\bar{x}) = 0$, ($\bar{x}$ is a rest point of (1.1) $\Longleftrightarrow x = \bar{x}$).

(iii) $\exists$ an $\eta > 0$, $\ni V(x) > 0$ whenever $x \in B_\eta(\bar{x})$, $x \neq \bar{x}$, where

$$B_\eta(\bar{x}) = \{x \in \mathbb{R}^n_+ \,|\, \|x - \bar{x}\| < \eta\}.$$

(iv) $\dot{V} \leq 0$ along the solution trajectories of (1.1)

(v) $V(x) \to \infty$ if either $x_i \to \infty$, or $\|x\| \to \infty$ or $x \to \partial \mathbb{R}^n_+$, [26,41].

Remark 1.2.

a. The requirements (ii) and (iii) of $D6$ imply that V is positive definite.

b. For global asymptotic stability, we require $\dot{V}(x) < 0$.

c. If V and $-\dot{V}$ are positive definite ($\dot{V}$ negative definite), with respect to $\bar{x}$, then $\bar{x}$ is globally asymptotically stable.

Now, $\dot{V}$ can be written in the form

$$\dot{V} = X^T A X = \langle AX, X \rangle \tag{1.17}$$

where

$$X = \begin{pmatrix} x_1 - \bar{x}_1 \\ \cdots \\ x_n - \bar{x}_n \end{pmatrix}$$

and $A(x, \bar{x})$ is a $n \times n$ symmetric matrix over $\mathbb{R}$, given by the expression

$$A(x, \bar{x}) = \begin{pmatrix} a_{11} & \cdots & a_{1n} \\ \cdots & & \\ a_{n1} & \cdots & a_{nn} \end{pmatrix}.$$

In particular, $\dot{V}$ is negative definite if $A(x, \bar{x})$ is negative definite.

Let D_k denote the sequence of (leading) principal minors of the matrix A. In particular,

$$D_1 = a_{11}, \qquad D_2 = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix},$$

$$D_3 = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}, \ldots, D_n = \begin{pmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ a_{n1} & a_{n2} & \cdots & a_{nn} \end{pmatrix}. \tag{1.18}$$

Theorem 1.2 [cf. Gantmacher [19]]. *The quadratic form* $A(x, \bar{x})$ *and consequently,* $\dot{V} = X^T AX$ *is negative definite if and only if the following inequalities hold:*

$$D_1 < 0, \quad D_2 > 0, \quad D_3 < 0, \ldots, (-1)^n D_n > 0. \tag{1.19}$$

Theorem 1.3 [cf. Bellman [7]]. *A necessary and sufficient condition for the quadratic form* $A(x, \bar{x})$ *to be negative definite is that all the characteristic roots (eigenvalues) of* $A(x, x)$ *be negative or have negative real parts.*

For the mechanics of construction of Liapunov functions for mathematical biology problems see Freedman [16], Shukla and Dubey [42], and Copasso and Forte [11].

1.3.2. Standard theorems

In this subsection, we present some theorems which will be used in the forthcoming chapters.

T_1 : Bendixon's Negative Criterion/Bendixson-du Lac Theorem:

Theorem 1.3. *Consider the system*

$$\begin{aligned} \dot{x}_1 &= F_1(x_1, x_2) \\ \dot{x}_2 &= F_2(x_1, x_2) \end{aligned} \tag{1.20}$$

on a simply connected domain $G \subset \mathbb{R}^2$. *Suppose*

(i) $F_1, F_2, \in C^1(G, \mathbb{R})$ *such that* F_1, F_2 *have continuous first partial derivatives* $\frac{\partial F_1}{\partial x_1}, \frac{\partial F_2}{\partial x_2}$ *on* G.

(ii) $\frac{\partial F_1}{\partial x_1} + \frac{\partial F_2}{\partial x_2}$ *does not change sign on* G, *and does not vanish identically in any open subset of* G.

Then there are no non-trivial closed paths (periodic solutions, limit cycles) in G [8].

Theorem 1.4. *Suppose,*

(i) $B(x_1, x_2) \in C^1(G, \mathbb{R})$

(ii) $\frac{\partial}{\partial x_1}\left[F_1(x_1, x_2)B(x_1, x_2)\right] + \frac{\partial}{\partial x_2}\left[F_2(x_1, x_2)B(x_1, x_2)\right]$ (1.21)

does not change sign or vanish identically on any open subset of the simply connected domain G.

then there are no closed orbits (periodic solutions, limit cycles) lying entirely in G [8].

T_2 : The Butler-McGehee Lemma [cf. 9,16,17]

Theorem 1.5. *Let* P *be an isolated hyperbolic closed invariant set with* $W^+(P)$ *and* $W^-(P)$ *its strong stable and unstable manifolds, respectively. Further, let* $P \in \Omega$, *where* Ω *is the omega limit set of some orbit.*

Then either (i) $\Omega = P$ *or* (ii) $W^+(P)\backslash\{P\}$ *and* $W^-(P)\backslash\{P\}$ *both are non-empty and there exists* $Q^+ \in W^+(P)\backslash\{P\}$ *and* $Q^- \in W^-(P)\backslash\{P\}$ *such that* $Q^+ \in \Omega$ *and* $Q^- \in \Omega$.

Remark 1.4. Persistence is equivalent to any orbit initiating in the interior of $\mathbb{R}^n_+$ not having any omega limit points on the boundary.

T_3 : Brouwer Fixed Point Theorem [cf. 8,48]

Theorem 1.6. *Let G be a simply connected planar open domain and T be a topological mapping of G into itself. If G is sense-preserving and there exists a point $x_0 \in G$ and a subsequence of the successive images*

$$x_1 = Tx_0, \quad x_2 = Tx_1, \ldots, x_n = Tx_{n-1} \tag{1.22}$$

which converge to a point in G, then T has a fixed point in G.

T_4 : Floquet Multipliers Theory

Consider the non-autonomous system

$$\left.\begin{aligned} \dot{x} &= F(t,x) & & \\ & & & \mathbb{R}_+ = [0,\infty) \\ x(t_0) &= x_0, & & \\ x,\, x_0 &\in \mathbb{R}^n, & & F \in C^1(\mathbb{R}_+ \times \mathbb{R}^n_+, \mathbb{R}^n) \\ F(t+w,x) &= F(t,x). & & \end{aligned}\right\} \tag{1.23}$$

Let $\psi = (\phi_1, \ldots, \phi_n)$ be a given periodic orbit or limit cycle of (1.23). Let the Jacobian matrix of linearization of (1.23) about ψ be given by

$$\begin{aligned} J_\psi &= DF(\psi) \\ &= \begin{pmatrix} m_{11} & \cdots & m_{1n} \\ \vdots & & \\ m_{n1} & \cdots & m_{nn} \end{pmatrix} = M = \{m_{ij}\}_{1 \le i,j \le n} \end{aligned} \tag{1.24}$$

such that J_ψ is locally integrable.

The Floquet multipliers are the eigenvalues of $X(\omega)$, where $X_{ij}(t)$ solves

$$\dot{X}(t) = M(t)X(t), \quad X(0) = I \tag{1.25}$$

$$\text{where} \qquad X(t) = \begin{pmatrix} X_{11}(t) & \dots & X_{1n}(t) \\ X_{n1}(t) & \dots & X_{nn}(t) \end{pmatrix}. \tag{1.26}$$

In general this is a tedious computation and sometimes only estimates are possible, unless the matrix J_ψ and consequently $X(t)$ has some zeroes.

Consider the following examples:

Example 1.1. Let

$$J_\psi = \begin{pmatrix} m_{11} & m_{12} & m_{13} \\ 0 & m_{22} & 0 \\ m_{31} & m_{32} & m_{33} \end{pmatrix}. \tag{1.27}$$

Then

$$X(t) = \begin{pmatrix} X_{11}(t) & X_{12}(t) & X_{13}(t) \\ 0 & X_{21}(t) & 0 \\ X_{31}(t) & X_{32}(t) & X_{33}(t) \end{pmatrix}. \tag{1.28}$$

By inspection,

$$X'_{2j} = m_{22} X_{2j} \tag{1.29}$$

$$X_{2j}(0) = I, \quad j = 1, 2, 3.$$

Then one Floquet multiplier of (1.27) is given by

$$\rho_2 = X_{22}(\omega) = e^{\int_0^\omega m_{22}\, dt}.$$

Example 1.2. Let

$$J_\psi = \begin{pmatrix} m_{11} & 0 \\ m_{21} & m_{22} \end{pmatrix}. \tag{1.29}$$

Then the Floquet multipliers are

$$\rho_1 = e^{\int_0^\omega m_{11}\,dt} \quad \text{and} \quad \rho_2 = e^{\int_0^\omega m_{22}\,dt}.$$

Theorem 1.7. *Consider the system*

$$\left.\begin{aligned} \dot{x}(t) &= A(t)x \\ x(t_0) &= x_0, \end{aligned}\right\} \tag{1.30}$$

where $A(t) = J_\psi$ *is a locally integrable* $n \times n$ *matrix such that*

$$A(t+\omega) = A(t).$$

Let ρ_i *denote the* i^{th} *Floquet multiplier. Then,*

(i) *All solutions* $x(t)$ *of* (1.30) *satisfy* $x(t) \to 0$ *as* $t \to \infty$ *if* $|\rho_i| < 1$, $i = \{1, \ldots, n\}$, *in which case* $x = \psi(t)$ *is asymptotically stable in the sense of Liapunov.*

(ii) *Some solution of* (1.30) *is a non-trivial* ω*-periodic solution if and only if* $\rho_1 = 1$ *for some* $i \in \{1, \ldots, n\}$.

(iii) *If however,* $|\rho_j| > 1$ *for some* $j \in \{1, 2, \ldots, n\}$, *then* $x = \psi(t)$ *is unstable.*

T_4: Hopf-Andronov-Poincare Bifurcation Theorem [cf. 24,39]

Theorem 1.8. *Let*

$$\left.\begin{aligned} \dot{x} &= F(x,\mu), \quad (\mu \text{ is a bifurcation parameter}) \\ x(t_0) &= x_0 \\ x \in \mathbb{R}^n, \quad \mu \in \mathbb{R}^p, &\quad F \in C^r(\mathbb{R}^n \times \mathbb{R}^p, \mathbb{R}^n). \end{aligned}\right\} \tag{1.31}$$

Suppose

(i) $F \in C^r$, $r \geq 5$ *on some sufficiently large open set* G *containing the equilibrium,* $(x, \mu) = (x_0, \mu_0) = \mathbb{P}_\mu$, *where* x_0 *is an isolated rest point of* $F(x, \mu)$.

(ii) $F(x, \mu) = 0$ *for some curve* $x = x(\mu)$ *with* $x(\mu) \in \eta(x_0, \mu_0)$, *a neighborhood of* (x_0, μ_0) *on* G.

(iii) *The Jacobian matrix* $J_\mu = D_x F(x_0, \mu_0)$ *has a pair of complex conjugate eigenvalues* λ *and* $\overline{\lambda}$ *such that*

$$\lambda(\mu) = \alpha(\mu) + i\beta(\mu), \quad \lambda(\mu) \in C^r$$

where

a. $\beta(\mu_0) > 0$

b. $\alpha(\mu_0) = 0$

c. $\frac{d}{d\mu}\,[\mathrm{Re}\,\lambda(\mu_0)] = \alpha'(\mu_0) \neq 0$ *(Transversality criterion)*
where $\mathbb{P}_{\mu=\mu_0}$ *is asymptotically stable.*

(iv) *The remaining* $n - 2$ *eigenvalues of* $J_\mu = D_x F(x_0, \mu_0)$ *have non-zero (preferably negative) real parts.*

Then, $\mathbb{P}_{\mu=\mu_0} = (x_0, \mu_0)$ *is a bifurcation point of the equilibrium,* $x = x_0$, *leading to a limit cycle for some small values of* $\mu \neq \mu_0$. *If* $\mu > \mu_0$ *the bifurcation is supercritical and if* $\mu < \mu_0$, *then the bifurcation is subcritical. If the bifurcation is all at* $\mu = \mu_0$, *there is a centre around* $x = x_0$ *and infinitely many neutrally stable concentric closed (periodic) orbits surrounding* $x = x_0$.

T_5: The Implicit Function Theorem [cf. 40,43]

Theorem 1.9. *Suppose* $f : \mathbb{R}^n \to \mathbb{R}^m$ *is continuously differentiable in an open*

set containing (x_0, y_0) *and* $f(x_0, y_0) = 0$. *Let* M *be the* $m \times m$ *matrix such that*

$$M = (D_{n+j} f^i(x_0)), \quad i \le i,\ j \le m,$$

If $\det M \neq 0$, *there is an open set* $A \subset \mathbb{R}^n$ *containing* x_0 *and an open set* $B \subset \mathbb{R}^m$ *containing* y_0, *with the following property: for each* $x \in A$ *there is a unique* $g(x) \in B$ *such that* $f(x, g(x)) = 0$. *The function* g *is differentiable.*

Theorem 1.10. *Assume that* $U \subset \mathbb{R}^n \times \mathbb{R}^k$ *is an open set and* $F : U \to \mathbb{R}^k$ *is a* C^r *function for some* $r \ge 1$. *Represent a point* $p \in U$ *by* $p = (x, y)$ *with* $x \in \mathbb{R}^n$ *and* $y \in \mathbb{R}^k$ *and the coordinate functions of* F *by* f_i,

$$F = (f_1, \ldots, f_k).$$

Assume that for some $(x_0, y_0) \in U$

$$\left(\frac{\partial f_i}{\partial y_j}(x_0, y_0)\right)_{1 \le i, j \le k} \tag{1.32}$$

is an invertible $k \times k$ *matrix (non-zero determinant). Let* $C = F(x_0, y_0) \in \mathbb{R}^k$. *Then there is an open set* V *containing* x_0, *and an open set* W *containing* y_0 *with* $V \times W \subset U$. *There is a* C^r *function* $h : V \to W$ *such that*

$$h(x_0) = y_0 \quad \text{and}$$

$$F(x, h(x)) = C \quad \text{for all} \quad x \in V.$$

Further, for each $x \in V$, $h(x)$ *is the unique* $y \in W$ *such that* $F(x, y) = C$.

T_6 : LaSalle's Invariance Principle and ODEs [41,37]

Consider system (1.1). Let $f : \mathbb{R}^n_+ \to \mathbb{R}^n$ satisfy a local Lipschitz condition.

Let $G \subset \mathbb{R}^n_+$ be any open set. Define a Liapunov function V on G such that $V : G \subset \mathbb{R}^n_+ \to \mathbb{R}^n$.

Theorem 1.11. *Suppose*

(i) V *is* C^1 *on* G *and bounded below.*

(ii) $\lim_{\|x\| \to \infty} V(x) = \infty$.

(iii) $\dot{V}(x) \leq 0$ *for every* $x \in G$ *along the solution trajectories of* (1.1).

(iv) $E = \{x \in \overline{G} \backslash \dot{V}(x) = 0\}$ *along the solution trajectories of* (1.1).

(v) M *is the largest invariant subset of* E.

Then all solutions of (1.1) *are bounded on* $\mathbb{R}_+ = [0, \infty)$ *and tend towards* M, *and consequently* M *is globally asymptotically stable.*

Remark 1.5. In many instances, the set M is determined as the rest point of (1.1). Further, if V is chosen so that $\dot{V}$ is continuous on $\overline{G}$, then E is closed.

T_7 : The Loziinski Matrix Measure and Stability [25]

Consider the system

$$\left.\begin{aligned} &\dot{x} = F(t,x), \quad x(t_0) = x_0 \\ &F \in C(\mathbb{R}_+ \times \mathbb{R}^n, \mathbb{R}) \end{aligned}\right\} \tag{1.33}$$

Define $DF(E(x_0)) = A(t)$ as the Jacobian matrix due to linearization of (1.33) in the neighborhood of the rest point $E(x_0)$.

Define the Loziinski Matrix measure $\mu(A)$ as follows:

$$\mu(A) = \lim_{h \to 0^+} \frac{\|I + hA\| - 1}{h} \tag{1.34}$$

where $\mu(A)$ exists as a finite number for every $A \in M_n$. Let $A \in C(\mathbb{R}_+, M_n)$ where M_n is the set of $n \times n$ matrices.

Theorem 1.12. *Consider the system*

$$\dot{x}(t) = A(t)x \tag{1.35}$$

where $A = \{a_{ij}(t)\}_{1 \le i,j \le n} \in C(\mathbb{R}_+, M_n)$. *Let*

$$\left.\begin{aligned} &\text{(i)} \quad \|x\| = \sup_i |x_i| \\ &\text{(ii)} \quad \|A\| = \sup_i |a_{ik}| \\ &\text{(iii)} \quad \mu(a) = \sup_i [Re\, a_{ii} + \sum_{k,k \ne i} |a_{ij}|]. \end{aligned}\right\} \tag{1.36}$$

If

(a) $\liminf_{t \to \infty} \int_0^t \mu(-A(s))ds = -\infty$ *then* (1.35) *is unstable,*

(b) $\limsup_{t \to \infty} \int_0^t \mu(A(s))ds < +\infty$ *then* (1.35) *is stable,*

(c) $\lim_{t \to -\infty} \int_0^t \mu(A(s))ds = -\infty$, *then* (1.35) *is asymptotically stable,*

(d) $\mu(A(t)) \le 0, \quad t \ge 0$, *then* (1.35) *is uniformly stable,*

(e) *there exists* $r > 0$, *such that* $\mu(A(t)) \le -r, \quad t > 0$, *then* (1.35) *is uniformly asymptotically stable.*

Remark 1.5. For other possible expressions for (1.36) see Kartsatos [25].

T_8 : **Massera's Theorem** [cf. V.A. Pliss, Nonlocal Problems of the Theory of Oscillations, Academic Press, New York, 1966, p. 156]

Theorem 1.13. *Consider the system*

$$\begin{aligned} \dot{x} &= F(t,x), \quad F(t+\omega,x) = F(t,x) \\ x(t_0) &= x_0, \\ x, x_0 &\in \mathbb{R}^2, \qquad F \in C^1(\mathbb{R}^2, \mathbb{R}^2). \end{aligned}$$

If all solutions are bounded, then there exists a periodic solution of the system with period ω.

T_9: The Poincaré-Bendixson Theorem

Theorem 1.14. *Consider the system*

$$\dot{x} = F(x),$$

$$x \in \mathbb{R}^2, \quad f : C^1(\mathbb{R}^2, \mathbb{R}^2).$$

Let $\mathcal{M}$ *be a positively invariant region for the vector field (of the system), containing a finite number of fixed points. Let* $p \in \mathcal{M}$, *and consider the* ω*-limit set of* p *denoted by* $\omega(p)$. *Then one of the following possibilities holds:*

i) $\omega(p)$ *is a fixed point (rest, critical equilibrium point)*

ii) $\omega(p)$ *is a closed orbit*

iii) $\omega(p)$ *consists of a finite number of fixed points* $p_1, \ldots, p_n$ *and orbits* γ *with the alpha limit set and omega limit set of* γ *being such that* $\alpha(\gamma) = p_i$ *and* $\omega(\gamma) = p_j$.

In particular if $\mathcal{M}$ *contains no fixed points (critical points), then it contains a limit cycle.*

T_{10} : The Routh-Hurwitz Criterion [3,12]

Consider the autonomous system

$$\dot{x} = F(x)$$

$$x \in \mathbb{R}^n, \quad F : C(\mathbb{R}^n, \mathbb{R}^n).$$

Let $A = DF(E(x_0))$ be the $n \times n$ matrix of linearization of the system around the fixed point $E(x_0)$, leading to the system

$$\dot{\xi} = A\xi, \quad \xi(0) = \xi_0. \tag{1.36}$$

Construct the characteristic polynomial equation $p(\lambda, A) = 0$ where

$$\begin{aligned} p(\lambda, A) &= \det(A - \lambda I_n) \\ &= \lambda^k + a_1\lambda^{k-1} + a_2\lambda^{k-2} + \cdots + a_k. \end{aligned} \tag{1.37}$$

Define k matrices as follows

$$H_1 = (a_1), \quad H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \quad H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix}$$

$$H_j = \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \\ a_{2j-1} & a_{2j-2} & a_{2j-3} & a_{2j-4} & \cdots & a_j \end{pmatrix},$$

$$H_k = \begin{pmatrix} a_1 & 1 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & & \\ 0 & 0 & 0 & \cdots & a_k \end{pmatrix}$$

where the (ℓ, m) term in the matrix H_j is

(i) $a_{2\ell-m}$ for $0 < 2\ell - m < k$

(ii) 1 for $2\ell - m$

(iii) 0 for $2\ell - m$ or $2\ell > k + m$.

Theorem 1.15. *The eigenvalues of* (1.36) *or* (1.37) *have negative real parts and consequently, the equilibrium* $E(x_0)$ *is locally asymptotically stable if and only if*

$$\det H_j > 0 \qquad (j = 1, 2, \ldots, k).$$

In particular for $k = 2, 3, 4$, *the criteria reduce to:*

$$k = 2 : a_1 > 0, \quad a_2 > 0$$

$$k = 3 : a_1 > 0, \quad a_3 > 0, \quad a_1 a_2 > a_3$$

$$k = 4 : a_1 > 0, \quad a_3 > 0, \quad a_4 > 0,$$
$$\text{and} \quad a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

1.4. Epilogue to the Introduction

It is emphasized that the notion to formulate mathematical models to study, analyze and predict the qualitative characteristics of human pathological processes is not a new venture. Euler and von Neumann did some work in physiology and neurobiology respectively. Cardiac conductions were studied by Mobitz, van der Pol, van der Mark, Wiener, and Rosenblueth during a period spanning 1920-1940.

In the forthcoming chapters generalized mathematical models will be constructed to study the cytokinetics of cancer and normal cells under chemotherapy and immunotherapy.

The mathematical models and computer simulations will not be structured to study chaos or fractals associated with certain cellular parametric configurations of neoplastic processes under chemotherapy or immunotherapy. The research on chaotic behavior of the models will be a future project. It must be emphasized that chaotic dynamics is an essential feature of cancer therapy and some treatment anomalies and periodic spontaneous cancer remissions or repopulations may be characteristic features of such processes. The study of such phenomena under the topic "Dynamical Diseases" has been done over the years by Mackey, [29,30,31,32].

The chapters are structured such that Chapter 2 deals with cancer chemotherapy. Sufficient criteria is obtained for the persistence of cancer, extinction of cancer cells and confinement of the cancer cells below a non-lethal threshold. Such clinical details are discussed in a model constructed by the author in [35]. In Chapter 3, mathematical models for cancer immunotherapy involving adoptively transferred immune cells or lymphocytes will be presented. Criteria for therapeutic success and failure will be discussed. In Chapter 4, the bio-clinical interpretations, implications and predictions of the models will be presented. As well, possible directions for future research will be given. Numerical examples will be used to illustrate results and will be done throughout the thesis. Our models will describe a tumor which remains localized and engages in competition with normal cells. The tumor can kill a patient without metastasizing: eg. cancers of the brain, liver and leukaemias.

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CHAPTER 2

A MATHEMATICAL MODEL OF CANCER TREATMENT BY CHEMOTHERAPY

2.1. Introduction

The ultimate role of mathematical modelling in cancer chemotherapy is to provide a basis for chemotherapy regimes and to make qualitative predictions about the dynamic evolution of the disease based on the cytokinetic parameters of the tumor/patient and the drug parametric configuration. Models for cancer chemotherapy can be deterministic or stochastic and at the same time can be cell cycle specific or non-specific. Cell cycle specific models have been developed and mathematically analysed in [3,12-16,20-21]. Cell cycle independent cancer cytokinetic chemotherapy models can be found in [7,21,22].

The deterministic theory of cancer cell dynamics and chemotherapy presupposes that the population sizes of normal and cancer cells are large enough to be described by continuous variables which are not affected by random cellular fluctuations. In this paper, cell-cycle independent cytokinetic cancer chemotherapy models are developed. The main thrust of this chapter is to model the interactions between normal cells, cancer cells and a chemotherapy agent in a confined area §2.2, under a single chemotherapy injection §2,3, continuous chemotherapy §2.4, and periodic chemotherapy introductions §2.5. In each case, we determined the equilibria and discussed their stabilities.

A simplified version of such models was considered in [11], who used Lotka-Volterra dynamics to model the competition between normal and cancer cells. A competitive model with periodic inputs was also considered in [17].

2.2. The Model

We take as our model of cancer treatment by chemotherapy a system of three ordinary differential equations of "ecological type", where $x_1(t)$ represents the concentration of normal cells, $x_2(t)$ the concentration of cancer cells, and $y(t)$ the concentration of chemotherapy agent in the affected region at time $t \geq 0$. We think of x_1 and x_2 as competing for nutrient, oxygen, etc. and we think of y as a predator capable of destroying both x_1 and x_2, but selectively is more lethal to x_2.

We suppose that the normal and cancer cells are in a state of competition when the chemotherapy agent is introduced into the body at time $t = 0$, and that the chemotherapy agent takes time τ to reach the affected tissues. We further suppose that the cancer is concentrated in a fixed region of the body. The case where the cancer is metastasize to other parts of the body is left to future work.

The model then takes the form

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)h(y) \tag{2.1a}$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - p_2(x_2)h(y) \tag{2.1b}$$

$$\dot{y} = \begin{cases} 0, & 0 \leq t < \tau \\ \varphi(x_1, x_2, y; t), & \tau \leq t, \end{cases} \tag{2.1c}$$

$$x_1(0) = x_{10} > 0, \quad x_2(0) = x_{20} > 0.$$

Here, $' = \frac{d}{dt}$, $B_i(x_i)$ and $D_i(x_i)$ are the birth and death rates respectively of the normal and cancer cells, $q_i(x_1, x_2)$ is the respective competition function, $p_i(x_i)$ is the "predator functional response" or cell-killing rate per agent of the chemotherapy, $h(y) = u(y)H(t-\tau)$, where $H(t)$ is the Heaviside unit step function, and $u(y)$ is the density dependent chemotherapy effect. Finally $\varphi(x_1, x_2, y, t)$ is the rule which governs the concentration of chemotherapy agent in the affected region. Clearly it depends on the injection strategy, and the body's reaction to the agent both before and after reaching the affected region.

Specifically we assume the following properties for the defined functions.

(H1): $B_i(0) = D_i(0) = 0, \quad 0 \le D_i'(0) < B_i'(0), \quad B_i'(x_i) > 0, \quad D_i'(x_i) > 0.$ There exists $K_i > 0$ such that $B_i(K_i) = D_i(K_i)$ and $B_i'(K_i) < D_i'(K_i)$, $i = 1, 2$. Further, $B_2(x) > B_1(x)$.

The above conditions imply that both normal cells and cancer cells can grow to their carrying capacities in the absence of other factors, but that cancer in general tend to grow more rapidly.

(H2): $q_i(x_1, x_2) \ge 0, \quad \frac{\partial q_i}{\partial x_j} \ge 0, \quad x_i \ge 0, \quad i, j = 1, 2.$

(H3): $p_i(0) = 0, \quad p_i'(x_i) > 0.$ Further $p_2'(x) > p_1'(x)$ due to the selectivity of

the chemotherapy agent.

(H4): $u(0) = 0, \quad u'(y) > 0$. Further $\lim_{y \to \infty} u(y) = \overline{u} < \infty$.

The existence of $\overline{u}$ is due to empirical observations of the effect of body enzymes on chemotherapy agents, [1,6,19, pp. 213-227].

We assume that the chemotherapy agent is initially injected at time $t = 0$ and initially reaches the affected region at time τ, hence the form of equation (2.1c). The function $\varphi(x_1, x_2, y, t)$ represents the rate of change of chemotherapy agent after time τ. We consider three strategies for chemotherapy treatment: I, a short infusion over time $\sigma > 0$: II, a continuous constant infusion: III, a periodically varying infusion.

According to the three above mentioned strategies, the function φ takes the following forms:

$$\text{I:} \quad \varphi(x_1, x_2, y, t) = \begin{cases} \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), & \tau \le t < \tau + \sigma, \\ -[\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), & \tau + \sigma \le t. \end{cases}$$

$$\text{II:} \quad \varphi(x_1, x_2, y, t) = \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), \qquad \tau \le t.$$

$$\text{III:} \quad \varphi(x_1, x_2, y, t) = f(t - \tau)\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), \quad \tau \le t,$$

– where $f(t + \omega) = f(t)$, for some $\omega > 0$ (the period).

Model (2.1) is analyzed throughout the remainder of this paper. However, before doing so, we need to consider the interaction of normal and cancer cells, when there is no treatment. This is done in the next section.

2.3. The No Treatment Case

In this section we consider the case where there is no treatment for the cancer, i.e. $\delta = 0$, $y = 0$ for all $t > 0$. Our model then takes the form

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) \tag{2.2a}$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2), \tag{2.2b}$$

with $x_1(0) \geq 0$, $x_2(0) \geq 0$. (Note that δ is the dose.)

The equilibria are $(0,0)$, $(K_1, 0)$, $(0, K_2)$, and possibly $(\tilde{x}_1, \tilde{x}_2)$. It is well known [2,9] that the dynamics of this system are trivial, i.e. all solutions approach an equilibrium. We assume that the dynamics are such that x_2 always wins in competition with x_1 (or there is no need for treatment). Hence in this case $(\tilde{x}_1, \tilde{x}_2)$ does not exist, and $(0, K_2)$ is a global attractor.

Computing the variational matrix of system (2.2) about $(0, K_2)$ gives that the eigenvalues are $\lambda_1 = B_2'(K_2) - D_2'(K_2) < 0$ and $\lambda_2 = B_1'(0) - D_1'(0) - K_2 q_1(0, K_2)$. Hence the condition that $(0, K_2)$ is a local attractor is that

$$B_1'(0) - D_1'(0) - K_2 q_1(0, K_2) < 0. \tag{2.3}$$

Hence if (2.3) is satisfied and the additional hypothesis that the system

$$\begin{aligned} B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) &= 0 \\ B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) &= 0 \end{aligned} \tag{2.4}$$

has no positive solutions, then by the trivial dynamics of competitive systems, $(0, K_2)$ is a global attractor. We assume that this is so in the remainder of the paper.

2.4. The Single Treatment Case

In this section we consider the case where $\varphi(x_1, x_2, y, t)$ is given by I. Then for $t \geq \tau + \sigma$, equation (2.1c) becomes

$$\dot{y} = -[\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]u(y) < 0, \tag{2.5}$$

and since there are no positive steady states, $\lim_{t \to \infty} y(t) = 0$ and so the equilibrium $(0, K_2, 0)$ is a global attractor.

Note that if instead of a single treatment, a finite number of discrete treatments are given, the net results are the same for this model.

2.5. The Continuous Treatment Case

Here we consider the case where chemotherapy is applied continuously. In this case $\varphi(x_1, x_2, y, t)$ is given by II and equation (2.1c) for $t \geq \tau$ is given by

$$\dot{y} = \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]u(y). \tag{2.6}$$

Then the equilibria for system (2.1) are as follows

$$\overline{E}(0,0,\overline{y}), \quad \widehat{E}_1(\widehat{x}_1,0,\widehat{y}_1), \quad \widehat{E}_2(0,\widehat{x}_2,\widehat{y}_2) \quad \text{and} \quad E^*(x_1^*,x_2^*,y^*),$$

where $\overline{y} =$ is the positive solution of $h(y) = \gamma^{-1}\delta e^{-k\tau}$, providing it exists.

In order for $\widehat{E}_1$ to exist, the algebraic system

$$\begin{aligned} B_1(x_1) - D_1(x_1) - p_1(x_1)u(y) &= 0 \\ \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y) &= 0 \end{aligned} \tag{2.7}$$

must have a positive solution. From $u(y) = \frac{\delta e^{-k\tau}}{\gamma+\eta_1 p_1(x_1)}$, this reduces to

$$B_1(x_1) - D_1(x_1) = \frac{\delta e^{-k\tau} p_1(x_1)}{\gamma + \eta_1 p_1(x_1)}. \tag{2.8}$$

We write this as $\varphi(x_1) = \psi(x_1)$.

Since $\varphi(0) = \varphi(K_1) = 0$ and $\varphi(x_1) > 0$ for $0 < x_1 < K_1$, and since $\psi(0) = 0$, $\psi(x_1) > 0$ for $x_1 > 0$, there will be a positive intersection of the curves $z = \varphi(x_1)$ and $z = \psi(x_1)$ provided $\psi'(0) < \varphi'(0)$. But $\psi'(0) = \gamma^{-1}\delta e^{-k\tau} p_1'(0)$ and $\varphi'(0) = B_1'(0) - D_1'(0)$. Hence we assume that

$$\gamma^{-1}\delta e^{-k\tau} p_1'(0) < B_1'(0) - D_1'(0), \tag{2.9}$$

which guarantees that $\widehat{E}_1$ exists. If we wish $\widehat{E}_1$ to be unique, we further assume that $z = \varphi(x_1)$ is concave down, i.e. that $B''(x_1) - D''(x_1) < 0$ for $0 \le x_1 \le K_1$. The above is illustrated in Fig. 2.1.

Note that if (2.9) is violated, it is still possible for $\widehat{E}_1$ to exist, but no easily stated sufficient condition is available.

Similarly, $\widehat{E}_2$ exists if

$$\gamma^{-1}\delta e^{-k\tau}p_2'(0) < B_2'(0) - D_2'(0). \tag{2.10}$$

We note that from a biological standpoint, neither $\overline{E}$ nor $\widehat{E}_2$ can occur, for in either case, there are no healthy cells left (presumably death has occurred or surgery has removed the organ in question).

Before discussing the existence question for E^*, the interior equilibrium, we analyze the stability of the boundary equilibria. The variational matrix $M(x_1, x_2, y)$ is of the form $M(x_1, x_2, y) = [m_{ij}(x_1, x_2, y)]_{3\times 3}$ where

$$\begin{aligned}
m_{11} &= B_1'(x_1) - D_1'(x_1) - x_1x_2q_{1x_1}(x_1, x_2) - x_2q_1(x_1, x_2) - p_1'(x_1)u(y)\\
m_{12} &= -x_1x_2q_{1x_2}(x_1, x_2) - x_1q_1(x_1, x_2)\\
m_{13} &= -p_1(x_1)u'(y)\\
m_{21} &= -x_1x_2q_{2x_1}(x_1, x_2) - x_2q_2(x_1, x_2)\\
m_{22} &= B_2'(x_2) - D_2'(x_2) - x_1x_2q_{2x_2}(x_1, x_2) - x_1q_2(x_1, x_2) - p_2'(x_2)u(y)\\
m_{23} &= -p_2(x_2)u'(y)\\
m_{31} &= -\eta_1p_1'(x_1)u(y)\\
m_{32} &= -\eta_2p_2'(x_2)u(y)\\
m_{33} &= -[\gamma + \eta_1p_1(x_1) + \eta_2p_2(x_2)]u'(y).
\end{aligned} \tag{2.11}$$

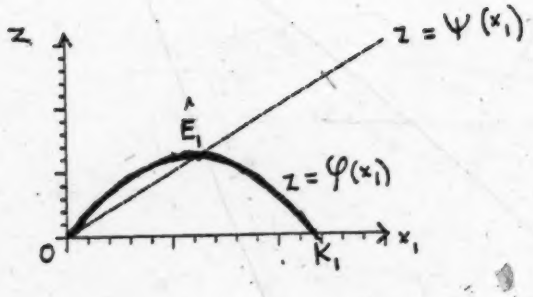

Figure 2.1

Existence of $\widehat{E}_1$. Solid line: $z = \varphi(x_1)$, dashed line: $z = \psi(x_1)$.

Letting the variational matrices about $\overline{E}_0, \widehat{E}_1$ and $\widehat{E}_2$ be $\overline{M}, \widehat{M}_1$ and $\widehat{M}_2$, respectively, we get that

$$\overline{M} = \begin{bmatrix} B_1'(0) - D_1'(0) \\ -p_1'(0)u(\overline{y}) & 0 & 0 \\ 0 & B_2'(0) - D_2'(0) \\ & -p_2'(0)u(\overline{y}) & 0 \\ -\eta_1 p_1'(0)u(\overline{y}) & -\eta_2 p_2'(0)u(\overline{y}) & -\gamma u'(\overline{y}) \end{bmatrix}$$

$$\widehat{M}_1 = \begin{bmatrix} B_1'(\widehat{x}_1) - D_1'(\widehat{x}_1) \\ -p_1'(\widehat{x}_1)u(\widehat{y}_1) & -\widehat{x}_1 q_1(\widehat{x}_1, 0) & -p_1(\widehat{x}_1)u'(\widehat{y}_1) \\ 0 & B_2'(0) - D_2'(0) \\ & -\widehat{x}_1 q_2(\widehat{x}_1, 0) - p_2'(0)u(\widehat{y}_1) & 0 \\ -\eta_1 p_1'(\widehat{x}_1)u(\widehat{y}_1) & -\eta_2 p_2'(0)u(\widehat{y}_1) & -[\gamma + \eta_1 p_1(\widehat{x}_1)]u'(\widehat{y}_1) \end{bmatrix}$$

$$\widehat{M}_2 = \begin{bmatrix} B_1'(0) - D_1'(0) \\ -\widehat{x}_2 q_1(0, \widehat{x}_2) - p_1'(0)u(\widehat{y}_2) & 0 & 0 \\ B_2'(\widehat{x}_2) - D_2'(\widehat{x}_2) \\ -p_2'(\widehat{x}_2)u(\widehat{y}_2) & -\widehat{x}_2 q_2(0, \widehat{x}_2) & -p_2(\widehat{x}_2)u(\widehat{y}_2) \\ -\eta_1 p_1'(0)u(\widehat{y}_2) & -\eta_2 p_2'(\widehat{x}_2)u(\widehat{y}_2) & -[\gamma + \eta_2 p_2(\widehat{x}_2)]u'(\widehat{y}_2) \end{bmatrix}.$$

From the above we can conclude the following:

(i) If $B_1'(0) - D_1'(0) - p_1'(0)u(\overline{y}) < 0$ and $B_2'(0) - D_2'(0) - p_2(0)u(\overline{y}) < 0$, then the chemotherapy agent kills all cells including the normal cells.

(ii) Suppose that at least

$$B_1'(0) - D_1'(0) - p_1'(0)u(\overline{y}) > 0, \tag{2.12}$$

so that the normal cells can possibly survive. Consider $\widehat{E}_1$. The eigenvalues of

$\widehat{E}_1$ are given by

$$\lambda = B_2'(0) - D_2'(0) - \widehat{x}_1 q_2(\widehat{x}_1, 0) - p_2'(0)u(\widehat{y}_1)$$

and the solutions of

$$\det \left| \lambda I - \begin{bmatrix} \widehat{\ell}_{11} & \widehat{\ell}_{12} \\ \widehat{\ell}_{21} & \widehat{\ell}_{22} \end{bmatrix} \right| = 0,$$

where,

$$\widehat{\ell}_{11} = B_1'(\widehat{x}_1) - D_1'(\widehat{x}_1) - p_1'(\widehat{x}_1)u(\widehat{y}_1)$$

$$\widehat{\ell}_{12} = -p_1(\widehat{x}_1)u'(\widehat{y}_1) < 0$$

$$\widehat{\ell}_{21} = -\eta_1 p_1'(\widehat{x}_1)u(\widehat{y}_1) < 0$$

$$\widehat{\ell}_{22} = -[\gamma + \eta_1 p_1(\widehat{x}_1)]u'(\widehat{y}_1) < 0.$$

This leads to the characteristic equation

$$\lambda^2 - (\widehat{\ell}_{11} + \widehat{\ell}_{22})\lambda + (\widehat{\ell}_{11}\widehat{\ell}_{22} - \widehat{\ell}_{12}\widehat{\ell}_{21}) = 0,$$

$$\text{or} \quad \lambda = \frac{1}{2}(\widehat{\ell}_{11} + \widehat{\ell}_{22}) \pm \frac{1}{2}\sqrt{(\widehat{\ell}_{11} - \widehat{\ell}_{22})^2 + 4\widehat{\ell}_{12}\widehat{\ell}_{21}}\,.$$

These latter eigenvalues are clearly real. Writing them as

$$\lambda = \frac{1}{2}(\widehat{\ell}_{11} + \widehat{\ell}22) \pm \frac{1}{2}\sqrt{(\widehat{\ell}_{11} + \widehat{\ell}_{22})^2 - 4(\widehat{\ell}_{11}\widehat{\ell}_{22} - \widehat{\ell}_{12}\widehat{\ell}_{21})}\,,$$

we see that they are both negative if and only if

$$\widehat{\ell}_{11} < 0, \text{ and } \widehat{\ell}_{11}\widehat{\ell}_{22} > \widehat{\ell}_{12}\widehat{\ell}_{21}. \tag{2.13}$$

We now wish to examine criteria for there to be no limit cycles in the $x_1 - y$, plane.

System (2.1) in the continuous treatment case, restricted to the $x_1 - y$ plane takes the form

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - p_1(x_1)u(y) \equiv f_1(x_1, y)$$

$$\dot{y} = \delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y) = g_1(x_1, y).$$

Using Dulac's negative criterion (Andronov et al., 1973, p. 413) we define

$$\mathcal{D}(x_1, y) = \frac{\partial}{\partial x}\left[p_1(x_1)^{-1} f_1(x_1, y)\right] + \frac{\partial}{\partial y}\left[p_1(x_1)^{-1} g_1(x_1, y)\right].$$

Then

$$\mathcal{D}(x_1, y) = \frac{d}{dx}\left[\frac{B_1(x_1) - D_1(x_1)}{p_1(x_1)}\right] - \left[\frac{\gamma + \eta_1 p_1(x_1)}{p_1(x_1)}\right] u'(y). \tag{2.14}$$

Cleary $\mathcal{D}(x_1, y) < 0$ for $x_1, y > 0$ if $\frac{B_1(x_1) - D_1(x_1)}{p_1(x_1)}$ is a decreasing function of x_1. This would be the case if the cancer interactions were modeled by $B_1(x_1) - D_1(x_1) = x_1 g_1(x_1)$ where $g_1(x_1)$ decreases and $p_1(x_1) = k_1 x_1$ or $p_1(x_1) = k$ [20, pp. 185-187, 21, pp. 152-156], or if e.g. $g(x_1) = 1 - bx_1$, $p_1(x_1) = \frac{x_1}{a + x_1}$, $ab > 1$.

In any of the above cases, or more generally if $\mathcal{D}(x_1, y) < 0$ for $x_1, y > 0$, then there are no periodic solutions in the $x_1 - y$ plane for system (2.14).

Similar mathematical statements may be said about the corresponding system in the $x_2 - y$ plane.

The final analysis in the $x_1 - x_2$ plane will involve criteria for $\widehat{E}_1$ to be globally asymptotically stable. For this purpose we utilize the Liapunov function

$$V(x_1, x_2, y) = x_1 - \widehat{x}_1 - \widehat{x}_1 \ell n \frac{x_1}{\widehat{x}_1} + \frac{1}{2} k_1 x_2^2 + \frac{1}{2} k_2 (y - \widehat{y}_1)^2, \tag{2.15}$$

where $k_1, k_2 > 0$ may be chosen later. Taking the derivative along solutions we get

$$\begin{aligned} \dot{V}(x_1, x_2, y) &= (x_1 - \widehat{x}_1)[g_1(x_1) - x_2 q_1(x_1, x_2) - r_1(x_1) u(y)] \\ &+ k_1 x_1^2 [g_2(x_2) - x_1 q_2(x_1, x_2) - r_2(x_2) u(y)] \\ &+ k_2 (y - \widehat{y}_1)[\delta e^{-k\tau} - (\gamma + \eta_1 x_1 r_1(x_1) + \eta_2 x_2 r_2(x_2)) u(y)], \end{aligned} \tag{2.16}$$

where we have set

$$\begin{aligned} B_i(x_i) - D_i(x_i) &= x_i g_i(x_i) \\ p_i(x_i) &= x_i r_i(x_i), \quad i = 1, 2. \end{aligned} \tag{2.17}$$

We note that $g_i(x_i)$ and $r_i(x_i)$ are well defined, and that

$$g_i(0) > 0, \quad g_i'(x_i) < 0, \quad r_i(0) \geq 0. \tag{2.18}$$

After some algebraic manipulations and utilizing the definition of $\widehat{x}_1$ and $\widehat{y}_1$, we may obtain that

$$\begin{aligned} \dot{V}(x_1, x_2, y) &= a_{11}(x_1 - \widehat{x}_1)^2 + 2a_{12}(x_1 - \widehat{x}_1)x_2 + 2a_{13}(x_1 - \widehat{x}_1)(y - \widehat{y}_1) \\ &+ a_{22} x_2^2 + 2a_{23} x_2 (y - \widehat{y}_1) + a_{33}(y - \widehat{y}_1)^2, \end{aligned} \tag{2.19}$$

where

$$
\begin{aligned}
a_{11} &= \frac{g_1(x_1) - r_1(x_1)u(\widehat{y}_1)}{x_1 - \widehat{x}_1} \\
a_{12} &= -\frac{1}{2}\, q_1(x_1, x_2) + \frac{1}{2}\, \frac{k_1[\widehat{x}_1 q_2(\widehat{x}_1, x_2) - x_1 q_2(x_1, x_2)]x_2}{x_1 - \widehat{x}_1} \\
a_{13} &= \frac{1}{2}\, r_1(x_1)\, \frac{[u(\widehat{y}_1) - u(y)]}{y - \widehat{y}} + \frac{1}{2}\, \frac{k_2\eta_1[\widehat{x}_1 r_1(\widehat{x}_1) - x_1 r_1(x_1)]}{x_1 - \widehat{x}_1} \\
a_{22} &= k_1[g_2(x_2) - \widehat{x}_1 q_2(\widehat{x}_1, x_2) - r_2(x_2)u(\widehat{y}_1)] \\
a_{23} &= k_1 x_2 r_2(x_2)\, \frac{[u(\widehat{y}_1) - u(y)]}{y - \widehat{y}_1} - k_2\eta_2 r_2(x_2)u(y) \\
a_{33} &= \frac{k_2[\delta e^{-k\tau} - (\gamma + \eta_1 \widehat{x}_1 r_1(\widehat{x}_1))u(y)]}{y - \widehat{y}_1}\,.
\end{aligned}
\tag{2.20}
$$

We first note that since $u(y)$ is an increasing function, then $a_{33} < 0$. However, it does not follows automatically that $a_{11} < 0$ and/or $a_{22} < 0$ unless $r_1(x)$ and/or $r_2(x_2)$ are nondecreasing functions, which in general may not be the case.

From the above, we have the following result.

Theorem 2.1. *Let the $a_{ij}(x_1, x_2, y)$ be defined by* (2.20). *Let $a_{11} < 0$ and $a_{22} < 0$ hold. Then if $k_1 > 0$ and $k_2 > 0$ can be chosen so that the matrix $A(x_1, x_2, y) \triangleq (a_{ij}(x_1, x_2, y))_{3\times 3}$ is negative definite, it follows that $\widehat{E}_1$ is globally asymptotically stable.*

The conditions of this theorem are very difficult to satisfy. But then, they correspond to the case where the cancer is completely destroyed, which is also a rare occurrence.

We may now address the question of an interior equilibrium in $x_1 - x_2 - y$ space.

Suppose that the $x_1 - y$ and $x_2 - y$ planes do not contain nontrivial periodic solutions. Suppose further that

$$B_2'(0) - D_2'(0) - \widehat{x}_1 q_2(\widehat{x}_1, 0) - p_2'(0)u(\widehat{y}_1) > 0 \tag{2.21a}$$

$$B_1'(0) - D_1'(0) - \widehat{x}_2 q_1(0, \widehat{x}_2) - p_1'(0)u(\widehat{y}_2) > 0 \tag{2.21b}$$

hold, and that $\widehat{E}_1$ and $\widehat{E}_2$ are asymptotically stable in their planes. Then by the techniques in [10], the system is persistent, and hence by the results in [4], the system is uniformly persistent and E^* exists. The stability of E^* is given by the eigenvalues of M^*, which are in general not computable in terms of tractable expressions.

However, in the case that E^* is asymptotically stable for low values of x_2^*, that case would corresond to the situation where the cancer is controlled at an acceptable low level.

2.6. The Periodic Treatment Case

In this section we consider model (2.1) where $\varphi(x_1, x_2, y, t)$ is given by case III, i.e.

$$\varphi(x_1, x_2, y, t) = f(t - \tau)\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]h(y), \quad \tau \le t \tag{2.22}$$

where $0 \le f(t + \omega) = f(t) \in C[0, \infty)$ for some $\omega > 0$ and $f(t) > 0$ on a set of

positive measure.

We first consider the existence and stability of periodic solutions in the $x_1 - y$ plane and then obtain criteria for the persistence and extinction of the cancer cells.

2.6.1. The $x_1 - y$ plane

We first show that under a mild assumption, all solutions initiating in the $x_1 - y$ plane are bounded and enter an attracting set in finite time.

In the $x_1 - y$ plane, system (2.1c) becomes

$$\begin{aligned} \dot{x}_1 &= B_1(x_1) - D_1(x_1) - p_1(x_1)u(y), \qquad x_1(0) = x_{10} \\ \dot{y} &= f(t-\tau)\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y), \quad y(0) = y_0, \quad t \geq \tau \end{aligned} \tag{2.23}$$

and let $0 \leq m \leq f(t) \leq M$.

Lemma 2.2. *Assume that*

$$\gamma \overline{u} > M\delta e^{-k\tau} \tag{2.24}$$

holds, where $\overline{u} = \lim_{t\to\infty} u(y)$. *Then*

(i) $x_1(t) \leq \max(K_1, x_{10})$, $y(t) \leq \max(\overline{y}, y_0)$, *where* $\overline{y}$ *is such that*

$$\gamma u(\overline{y}) = M\delta e^{-k\tau} \tag{2.25}$$

(ii) $\limsup_{t\to\infty}(x_1(t), y(t)) \subset \mathcal{A}$ *where*

$$\mathcal{A} = \{(x_1, y) : 0 \le x_1 \le K_1,\ 0 \le y \le \overline{y}\}.$$

Assume that the treatment begins at $t = 0$ and here $y_0 > 0$.

Proof. If $x_{10} = 0$, then $x_1(t) \equiv 0$. If $x_{10} > 0$, then $\dot{x}_1 < B_1(x_1) - D_1(x_1)$, and so by standard comparison theory, since $B_1(K_1) = D_1(K_1)$ and $B_1(x_1) < D_1(x_1)$ for $x_1 > K_1$, we have that $x_1(t) \le \max(K_1, x_{10})$. Further, since $\dot{x}_1 < 0$ for $x_1 > K_1$, we get that $\limsup_{t\to\infty} x_1(t) \le K_1$.

Now

$$\dot{y} = f(t-\tau)\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1)]u(y)$$

$$< M\delta e^{-k\tau} - \gamma u(y).$$

Hence by (2.25) and standard comparison theory, $y(t) \le \max(\overline{y}, y_0)$ and when $y = \overline{y}$, then $\dot{y} < 0$, we get that $\limsup_{t\to\infty} y(t) \le \overline{y}$, and thus the lemma is proved.

□

The above show that all solutions initiating in the positive octant are eventually uniformally bounded (and hence system 2.23 is dissipative) and so all solutions are continuable for positive t. Hence by Massera's theorem [18] and the fact that system 2.23 has no equilibria, we have shown the following.

Theorem 2.3. *If inequality* (2.24) *holds, then there exists a nonnegative periodic*

solution of (2.23) *of period* ω.

□

Unfortunately, by the same token, the equation

$$\dot{y} = f(t-\tau)\delta e^{-k\tau} - \gamma u(y) \tag{2.26}$$

has a periodic solution, $y = \psi_0(t)$, $\psi_0(t+\omega) = \psi_0(t)$ and so the periodic solution of (2.23) found by Theorem 2.3 could be $(0, \psi_0(t))$, which is not interior to the $(x_1 - y)$ plane.

We now show that $\psi_0(t)$ is unique.

Theorem 2.4. *Let* $y_1(t)$, $y_2(t)$, *be periodic solutions of period* ω *of* (2.26) *such that* $y_i(\tau) = \psi_0(\tau)$, $i = 1, 2$. *Then* $y_1(t) \equiv y_2(t)$.

Proof. Let $y(t) = y_1(t) - y_2(t)$. Then $\dot{y}(t) = \gamma(u(y_2) - u(y_1))$ and $y(t) = \gamma \int_\tau^t (u(y_2) - u(y_1))dt$. Since $u(y_i)$ is differentiable (and hence Lipschitzian) there exists $L > 0$ such that $|u(y_2) - u(y_1)| \leq L|y_1 - y_2|$. Hence $|y(t)| \leq \gamma \int_\tau^t L|y(s)|ds$, and so by Gronwall's inequality, $y(t) \equiv 0$.

□

Having established the above, we can now formulate criteria for there to exist (and not to exist) an interior (to the $x_1 - y$ plane) periodic solution.

Theorem 2.5. *Define* $\mu_0 = \frac{1}{\omega} \int_0^\omega u(\psi_0(s))ds$, *where* ψ_0 *is the unique nontrival*

ω *periodic solution of* (2.26). *Let*

$$\nu \triangleq \max_{0 \le x_1 \le K_1} [B_1'(x_1) - D_1'(x_1) - p_1'(x_1)u(\beta)], \tag{2.27}$$

where $\beta = \min_{t \subset [0,\omega]} \psi_0(t)$. *Then:*

(i) *If* $\mu_0 > \frac{B_1'(0) - D_1'(0)}{p_1'(0)}$, *then the* ω*-periodic solution* $(0, \psi_0(t))$ *of* (2.23) *is asymptotically stable.*

(ii) *If in addition* $\nu < 0$, *then* $(0, \psi_0(t))$ *is globally asymptotically stable.*

Proof of (i). The Jacobian matrix due to linearization about $(0, \psi_0)$ is

$$M_0 = J_F(0, \psi_0) = \begin{bmatrix} B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0) & 0 \\ -\eta_1 p_1'(0)u(\psi_0) & -\gamma u'(\psi_0) \end{bmatrix}.$$

The Floquet multipliers are

$$\rho_1 = e^{\int_0^\omega [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(s))]ds}$$

and

$$\rho_2 = e^{-\int_0^\omega \gamma u'(\psi_0(s))ds} \quad \text{where} \quad u'(\psi_0(s)) > 0$$

which implies that $|\rho_2| < 1$.

Hence $(0, \psi_0)$ is locally asymptotically stable if

$$\int_0^\omega [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(s))]ds < 0, \tag{2.28}$$

and unstable if

$$\int_0^\omega [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(s))]ds > 0. \tag{2.29}$$

However (2.28) and (2.29) can be written as

$$\mu_0 > \frac{B_1'(0) - D_1'(0)}{p_1'(0)} \Longrightarrow \quad \text{stability} \tag{2.30}$$

$$\mu_0 < \frac{B_1'(0) - D_1'(0)}{p_1'(0)} \Longrightarrow (0, \psi_0) \quad \text{is unstable.} \tag{2.31}$$

Proof of (ii). Let $F(x_1) = B_1(x_1) - D_1(x_1) - p_1(x_1)u(\beta)$. Then $F \in C^1([0,\omega] \times [0,K_1], \mathbb{R}_+)$ and $F(0) = 0$. Clearly ν as defined in (6.6) satisfies $\nu = \max_{x_1 \in [0,K_1]} F'(x_1)$. Then

$$\begin{aligned}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - p_1(x_1)u(y) \\
&\leq F(x_1) \\
\frac{\dot{x}_1}{x_1} &\leq \frac{F(x_1)}{x_1} \quad x_1 \in (0, K_1] \\
&\leq \max_{x_1 \in [0,K_1]} F'(x_1) \\
&\leq \nu.
\end{aligned}$$

Hence $x_1 \leq x_{10} e^{\nu t}$.

If $\nu < 0$ then $\lim_{t \to +\infty} x_1(t) = 0$.

Hence all solutions initiating in the interior approach the y-axis, and so

approach $(0, \psi_0(t))$.

□

We now wish to obtain criteria for there to exist an interior periodic solution. We first show that if $\mu_0 < 0$, then $x_{10} > 0 \Longrightarrow \exists \theta > 0 \ni \limsup_{t\to\infty} x_1(t) \geq \theta$.

To see this consider the system linearized about $x_1 = 0$, $y = \psi_0(t)$. Then the linearized system can be written as

$$\dot{v} = [B_1'(0) - D_1'(0) - p_1'(0)u(\psi_0(t))]v$$

$$\dot{w} = -\eta_1 p_1'(0)u(\psi_0(t))v - \gamma u'(\psi_0(t))w.$$

Hence $v(t) = v_0 e^{[B_1'(0)-D_1'(0)]t} e^{-p_1'(0)\int_0^t u(\psi_0(s))ds}$. We are given that $B_1'(0) - D_1'(0) > 0$. Hence if $\mu_0 < 0$, by standard persistence theory [4,10] this statement holds true.

We then reexamine Theorem (2.3) for large $t > 0$ in the region $x_1 \geq \theta$, $y \geq 0$. Then Massera's Theorem gives a nontrivial positive periodic solution.

By the above we have shown the following corollary.

Corollary 2.6. *Let* (2.24) *and* $\mu_0 < 0$ *hold. Then there exists a nontrivial* ω*-periodic solution lying in the region* $\{(x_1, y) : \theta \leq x_1 \leq K_1, \quad 0 < y \leq \bar{y}\}$.

We have now established the existence of a positive periodic solution interior to the positive quadrant of the $x_1 - y$ plane. Mathematically we could also establish such a periodic solution in the $x_2 - y$ plane in an entirely similar manner,

but physiologically, an organ containing only cancer cells and no normal cells means that the organism no longer exists.

At this time, we wish to discuss the stability of the periodic solution found above. In order to do this, we recall the definition of Lozinskii measure [5, p. 41] which in the case of a 2×2 matrix (a_{ij}) is

$$\mu(A) = \max\{a_{11} + |a_{21}|, a_{22} + |a_{12}|\}.$$

Theorem 2.7. *Let*

$$\begin{aligned} \tilde{\mu}(t) \triangleq \max\{&B_1'(\varphi_1(t)) + D_1'(\varphi_1(t)) \\ &+ (\eta_1 - 1)p_1'(\varphi_1(t))u(\psi(t)),\ [\gamma + (\eta_1 - 1)p_1(\varphi_1(t))]u'(\psi(t))\}, \end{aligned} \tag{2.32}$$

where $(\varphi_1(t), \psi(t))$ *is the periodic solution found by Theorem* 2.5.

(i) *If* $\int_0^\infty \tilde{\mu}(s)ds = -\infty$, *then* $(\varphi_1(t), \psi(t))$ *is asymptotically stable.*

(ii) *If* $\tilde{\mu}(t) \leq -\alpha < 0$, *then* $(\varphi_1(t), \psi(t))$ *is uniformly asymptotically stable.*

Proof. Let $A(t)$ be the Jacobian matrix of system (2.23) about $(\varphi_1(t), \psi(t))$. Then
$A(t) = (a_{ij}(t))$ where

$$a_{11}(t) = B_1'(\varphi_1(t)) - D_1'(\varphi_1(t)) - p_1'(\varphi_1(t))u(\psi(t))$$

$$a_{12}(t) = -p_1(\varphi_1(t))u'(\psi(t))$$

$$a_{21}(t) = -\eta_1 p_1'(\varphi_1(t))u(\psi(t))$$

$$a_{22}(t) = -[\gamma + \eta_1 p_1(\varphi_1(t))]u'(\psi(t)).$$

Then the function $\tilde{\mu}(t)$ defined by (2.32) is just the Lozinskii measure, $\mu(A(t))$. The theorem then follows from the stability criteria of [5, p. 59].

□

In the following corollary, we give explicit criteria for $\mu(A(t)) < 0$ and therefore for $(\varphi_1(t), \psi(t))$ to be uniformly asymptotically stable.

Corollary 2.8. *Define* $\overline{x}_1 = \sup\{x_1 : B_1'(x_1) = D_1'(x_1)\}$. *Assume the following hold:*

(H): $\eta_1 < 1$, $\overline{x}_1 < \varphi_1(t) < K_1$, $u'(y) \geq u_0'$ *(where* u_0' *is a positive constant),* $\gamma < (1-\eta_1)p_1(\overline{x}_1)$. *Define* $\overline{\beta} = \min |B_1'(\varphi_1(t)) - D_1'(\varphi_1(t))|$. *Then* $\mu(A(t)) = \tilde{\mu}(t) \leq -\alpha < 0$.

Proof. Since $\eta_1 < 1$ and $\varphi_1(t) > \overline{x}_1$, then

$$B_1'(\varphi_1) - D_1'(\varphi_1) + (\eta_1 - 1)p_1'(\varphi_1)u(\psi) < B_1'(\varphi_1) - D_1'(\varphi_1) \leq -\overline{\beta}.$$

Further, $[\gamma + (\eta_1 - 1)p_1(\varphi_1)] \leq [\gamma + (\eta_1 - 1)p_1(\overline{x}_1)] < 0$ since $\gamma < (1-\eta)p_1(\overline{x}_1)$. Hence $[\gamma + (\eta_1 - 1)p_1(\varphi_1)]u'(\psi) \leq [\gamma + (\eta_1 - 1)p_1(\overline{x}_1)]u_0' < 0$. Therefore, taking

$\alpha = \min\{\overline{\beta}, |\overline{\gamma} + (\eta_1 - 1)p_1(\overline{x}_1)|u_0'\}$, the corollary is proved.

□

2.6.2. $x_1 - x_2 - y$ space

We now consider the dynamics of chemotherapy agent interaction with both normal and cancer cells. Our first result gives criteria for the cancer to be completely eliminated from the site under consideration. Since physiologically this is not the most likely outcome, the mathematical criteria are fairly restrictive, as expected. For easy reference in this section, we repeat system (2.1) with $\varphi(t, x_1, x_2, y)$ given by (2.22) for $t > \tau$:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)u(y) \tag{2.33a}$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - p_2(x_2)u(y) \tag{2.33b}$$

$$\dot{y} = f(t-\tau)\delta e^{-k\tau} - [\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2)]u(y). \tag{2.33c}$$

Theorem 2.9. *Let* $\underline{\sigma}, \overline{\sigma}, \overline{y}$ *be such that*

$$\underline{\sigma} y \le u(y) \le \overline{\sigma} y, \quad \underline{\sigma}\,\overline{y} \ge M\delta e^{-k\tau}, \tag{2.34}$$

holds for $0 \le y \le \overline{y}$. *Let*

$$\overline{\Gamma} = \max_{0 \le x_2 \le K_2} (B_2'(x) - D_2'(x_2)), \quad \underline{\Pi} = \min_{0 \le x_2 \le K_2} p_2'(x_2).$$

Let $\underline{U} = \frac{m\delta e^{-k\tau}\underline{\sigma}}{[\gamma + \eta_1 p_1(K_1) + \eta_2 p_2(K_2)]\overline{\sigma}}$, *where* $0 < m \le f(t) \le M$. *Then if* $\overline{\Gamma} - \underline{\Pi}\,\underline{U} < 0$, $x_2(t) \to 0$ *as* $t \to \infty$.

Proof. From (2.33c) and (2.34) we have that

$$m\delta e^{-k\tau} - [\gamma + \eta_1 p_1(K_1) + \eta_2 p_2(K_2)]\overline{\sigma} y \le \dot{y} \le M\delta e^{-k\tau} - \gamma \underline{\sigma} y.$$

Since $y(\tau) = 0$, for $t > \tau$ we obtain by Kanke's comparison theorem

$$\frac{m\delta e^{-k\tau}}{[\gamma + \eta_1 p_1(K_1) + \eta_2 p_2(K_2)]\overline{\sigma}} \le y \le \frac{m\delta e^{-k\tau}}{\underline{\sigma}},$$

i.e. $\underline{U} \le u(y) \le M\delta e^{-k\tau}$.

From (2.33b), we have that

$$\begin{aligned} \dot{x}_2 &\le B_2(x_2) - D_2(x_2) - p_2(x_2)u(y) \\ &\le B_2(x_2) - D_2(x_2) - p_2(x_2)\underline{U} \equiv F(x_2). \end{aligned}$$

But $F(0) = 0$, and $F'(x_2) = B_2'(x_2) - D_2'(x_2) - p_2'(x_2)\underline{U} \le \overline{\Gamma} - \underline{\Pi}\underline{U} < 0$, and so $x_2(t) \to 0$ as $t \to \infty$.

□

In an analogous manner, the following theorem may be proved.

Theorem 2.10. *Let* $\overline{\Gamma}_\varepsilon = \max_{\varepsilon \le x_2 \le K_2} (B_2'(x_2) - D_2'(x_2))$, $\underline{\Pi}_\varepsilon = \min_{\varepsilon \le x_2 \le K_2} p_2'(x_2)$. *Then if* $\overline{\Gamma}_\varepsilon - \underline{\Pi}_\varepsilon \underline{U} < 0$, $\limsup_{t \to \infty} x_2(t) \le \varepsilon$.

□

Note that $\overline{\Gamma}_\varepsilon$ is a nonincreasing function of ε whereas $\underline{\Pi}_\varepsilon$ is a nondecreasing function of ε.

This last theorem gives a criterion for the control of the cancer cells, i.e. a criterion to eventually force the cancer level to below a prescribed level. From another point of view, for a given $f(t)$, the value of ε such that $\overline{\Gamma}_\varepsilon - \underline{\Pi}_\varepsilon \underline{U} = 0$ is an upper limit to the level of eventual cancer concentration.

Our next goal is to obtain criteria for the existence of a periodic solution in $x_1 - x_2 - y$ space. Of course if the hypotheses of Theorem 2.10 are satisfied, this periodic solution will have only small values of x_2 for small $\varepsilon > 0$.

The results here depend on the ability of the solution $(\varphi_1(t), 0, \psi(t))^T$ to change stability. Hence we require the following lemma.

For convenience of notation, let

$$B_2(x_2) = b\widehat{B}_2(x_2) \tag{2.35}$$

and

$$g(t,b) = b\widehat{B}_2'(0) - D_2'(0) - \varphi_1(t)q_2(\varphi_1(t),0) \quad - p_2'(0)u(\psi(t)).$$

Lemma 2.11. *Let $(\varphi_1(t), 0, \psi(t))^T$ be the periodic solution in the $x_1 - y$ plane found in Theorem 2.5 and assume $\int_0^\infty \widetilde{\mu}(t)dt = -\infty$. Then this periodic solution is asymptotically stable (resp. unstable) if*

$$\int_0^\infty g(t,b)dt < 0 \quad (\text{resp. } > 0).$$

Proof. If one computed the variational matrix about this periodic solution, one

gets from $\int_0^\infty \tilde{\mu}(t)dt = -\infty$, that it is stable in the $x_1 - y$ plane. The second row of this matrix has a nonzero term only in the 22 spot, and it is $g(t,b)$. Hence the Floquet multiplier corresponding to the x_2 direction is $e^{\int_0^\omega g(t,b)dt}$, giving the theorem.

□

Note that $g(t,0) < 0$, whereas $g(t,+\infty) = +\infty$. Hence $\int_0^\omega g(t,b)dt$ can be both negative and positive for various b. Further, since $g(t,b)$ is a strictly increasing function of b, there exists a unique b_0 such that

$$\int_0^\omega g(t,b_0)dt = 0. \tag{2.36}$$

The technique used in establishing criteria for the existence of a three-dimensional positive periodic solution is to bifurcate from the planar periodic solution to the interior, with b as the bifurcation parameter. As b passes through b_0, since the planar solution loses its stability, one would expect under the right circumstances for a bifurcation into a stable interior periodic solution.

Unfortunately, the criteria for this to occur are very complicated and encompass several cases to consider involving critical cases of the implicit function theorem. We discuss these in some detail in the Appendix. However, for the reader not interested in the gruesome details, we hereby state that criteria do exist guaranteeing such a positive periodic solution.

As to the stability of this solution, it involves a further degree of difficulty and is not discussed here.

2.7. Numerical Examples

In this section we describe some examples to illustrate some of our results. In the first two examples there is a linear dependence on y, whereas in the next four examples, there is a Michaelis-Menten dependence on y. In either case, parameter values are chosen to illustrate the mathematical results, and may not correspond to any actual medical possibility.

2.7.1. Examples 1-2 (Adjuvant chemotherapy)

In this section, both examples will be of the form

$$\begin{aligned} \dot{x}_1 &= a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 - a_{14}x_1y \\ \dot{x}_2 &= a_{21}x_2 - a_{22}x_2^2 - a_{23}x_1x_2 - a_{24}x_2y \\ \dot{y} &= a_3f(t) - (a_{33} + a_{34}x_1 + a_{35}x_2)y. \end{aligned} \tag{2.37}$$

Example 1. In this example we set

$$a_{11} = 3.645, \quad a_{12} = .0025, \quad a_{13} = .0025, \quad a_{14} = .00807$$

$$a_{21} = 6.405, \quad a_{22} = .008, \quad a_{23} = .00075, \quad a_{24} = .00985$$

$$a_3 = 4500, \quad a_{33} = .02, \quad a_{34} = .125, \quad a_{35} = .225, \quad f(t) = 1.$$

The initial conditions are $x_{10} = 1000$, $x_{20} = 200$, $y_0 = 0$.

This example represents a constant input of chemotherapy agent. Very quickly normal cells, cancer cells and the chemotheraphy agent go to a steady

state (see Fig. 2.2).

Example 2. The constant and initial conditions are the same as in Example 1. However in this example, $f(t)$ is a periodic function, $f(t) = 5 + 5 \sin \frac{5}{2} t$.

The solution rapidly approaches a periodic function (see Fig. 2.3) which looks to be globally stable.

2.7.2. Examples 3-6. In this subsection all examples are of the form

$$\dot{x}_1 = a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 - \frac{a_{14}x_1y}{1+y}$$

$$\dot{x}_2 = a_{21}x_2 - a_{22}x_2^2 - a_{23}x_1x_2 - \frac{a_{24}x_2y}{1+y}$$

$$\dot{y} = a_3 f(t) - (a_{33} + a_{34}x_1 + a_{35}x_2)\frac{y}{1+y}.$$

Example 3. In this example the coefficients are

$$a_{11} = 3.645, \quad a_{12} = .0025, \quad a_{13} = .00255, \quad a_{14} = .00807$$

$$a_{21} = 6.405, \quad a_{22} = .008, \quad a_{23} = .00075, \quad a_{24} = .01985,$$

$$a_3 = 450, \quad a_{33} = .02, \quad a_{34} = .4125, \quad a_{35} = .5225,$$

$$x_{10} = 1000, \quad x_{20} = 200, \quad y_0 = 0.$$

In this example $f(t) \equiv 1$ is the constant input. All solutions rapidly approach a constant steady state (see Fig. 2.4).

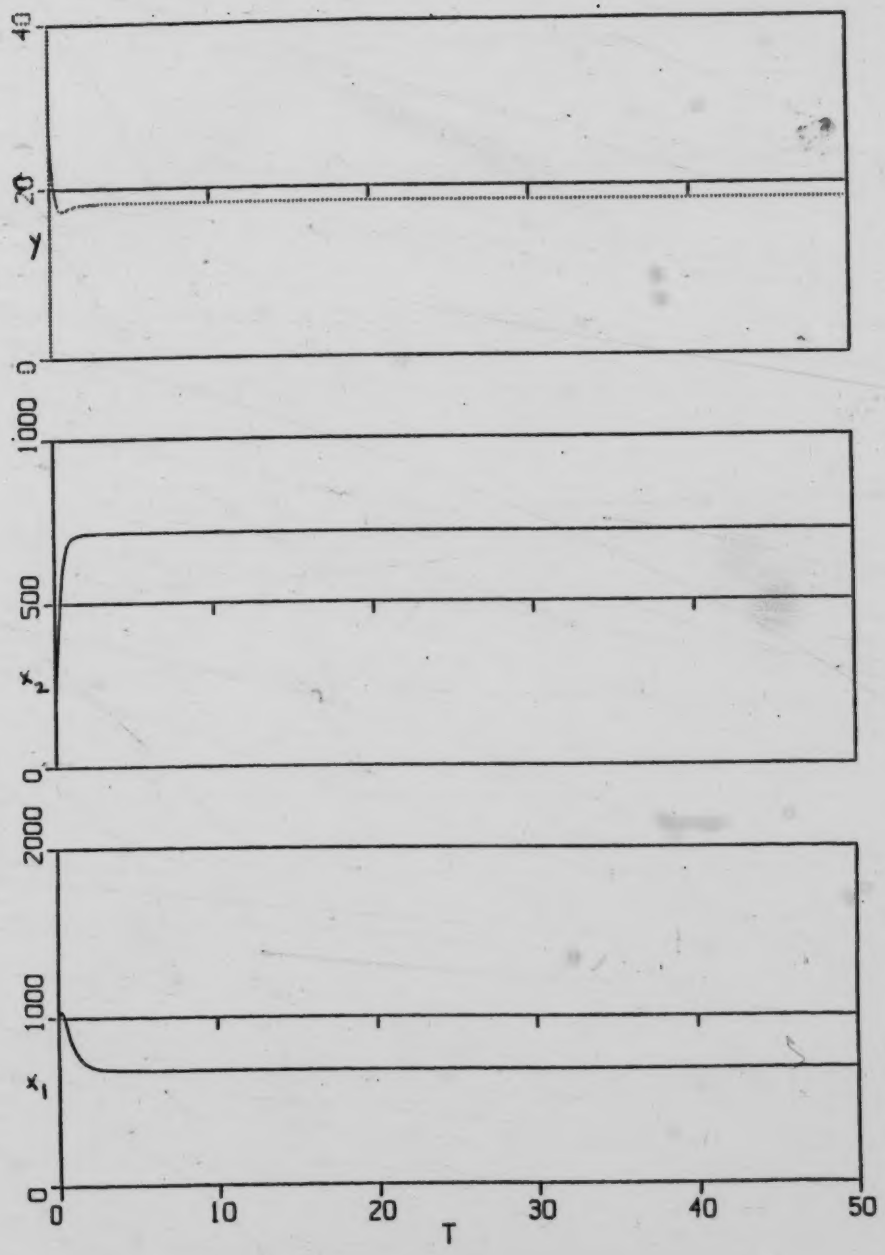

Figure 2.2
Constant chemotherapy input with linear uptake.
Constants, initial conditions and $f(t)$ given in text.

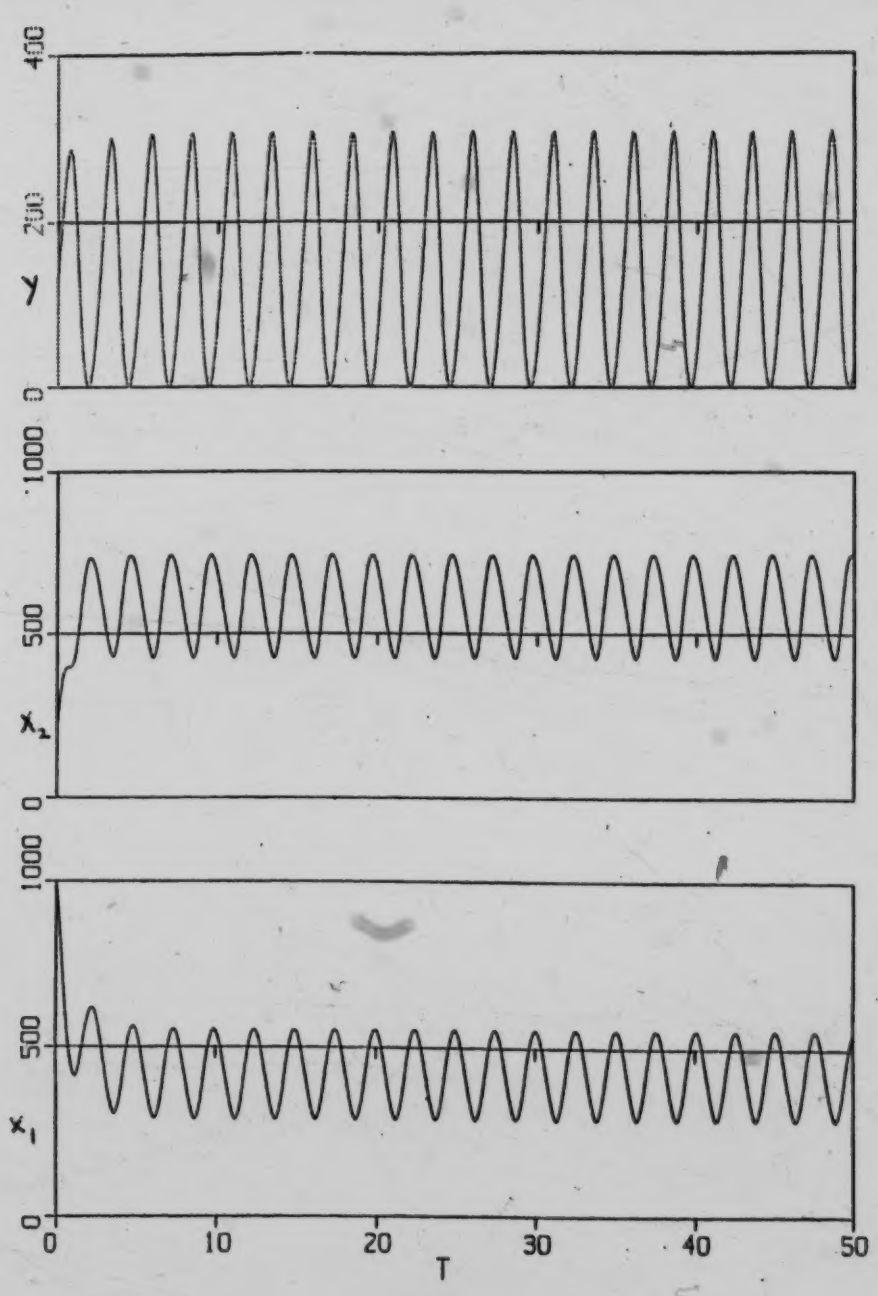

Figure 2.3

Periodic chemotherapy input with linear uptake.
Constants, initial conditions and $f(t)$ given in text.

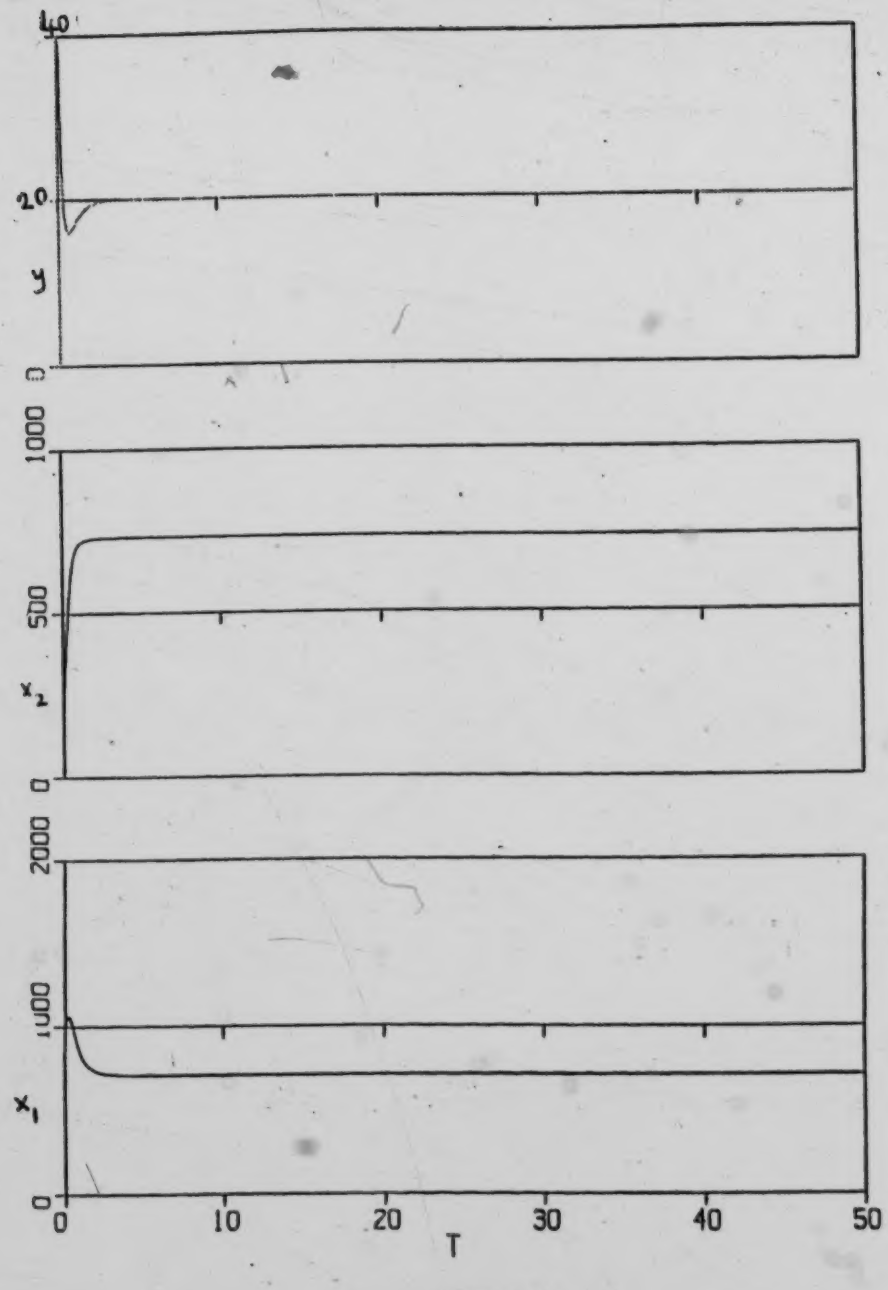

Figure 2.4

Constant chemotheraphy input with Michaelis-Menton uptake.
Constants, initial conditions and $f(t)$ given in text.

Example 4. Here, $f(t)$ is a periodic function of period 2 such that

$$f(t) = \begin{cases} 1, & 0 \le t \le .5 \\ 0, & .5 < t \le 2. \end{cases}$$

All solutions rapidly approach a steady state which is periodic in x_2 with small amplitude and constant in x_1 (see Fig. 2.5). The value of the constants are

$$a_{11} = 1.98, \quad a_{12} = .005, \quad a_{13} = .0055, \quad a_{14} = .00025,$$

$$a_{21} = 2.5, \quad a_{22} = .05, \quad a_{23} = .005, \quad a_{24} = .25$$

$$a_3 = 800, \quad a_{33} = .45, \quad a_{34} = 1.25, \quad a_{35} = 2.25.$$

The initial conditions are $x_{10} = 1000, \quad x_{20} = 100, \quad y_0 = 0.$

Example 5. In this example

$$a_{11} = 1.98, \quad a_{12} = .005, \quad a_{13} = .085, \quad a_{14} = .07,$$

$$a_{21} = 3.5, \quad a_{22} = .008, \quad a_{23} = .01, \quad a_{24} = .085,$$

$$a_3 = 1140, \quad a_{33} = .05, \quad a_{34} = .45, \quad a_{35} = .9.$$

Here $f(t)$ is a periodic function similar to the last example, but with period 3 such that $f(t) = \begin{cases} 1, & 0 \le t \le .5 \\ 0, & 5 < t \le 3. \end{cases}$ Initial conditions are $x_{10} = 1000, \quad x_{20} = 15, \quad y_0 = 0$. From Fig. 2.6, one can see that the cancer takes over, i.e. it approaches a period function of high values whereas the normal cells are driven extinct.

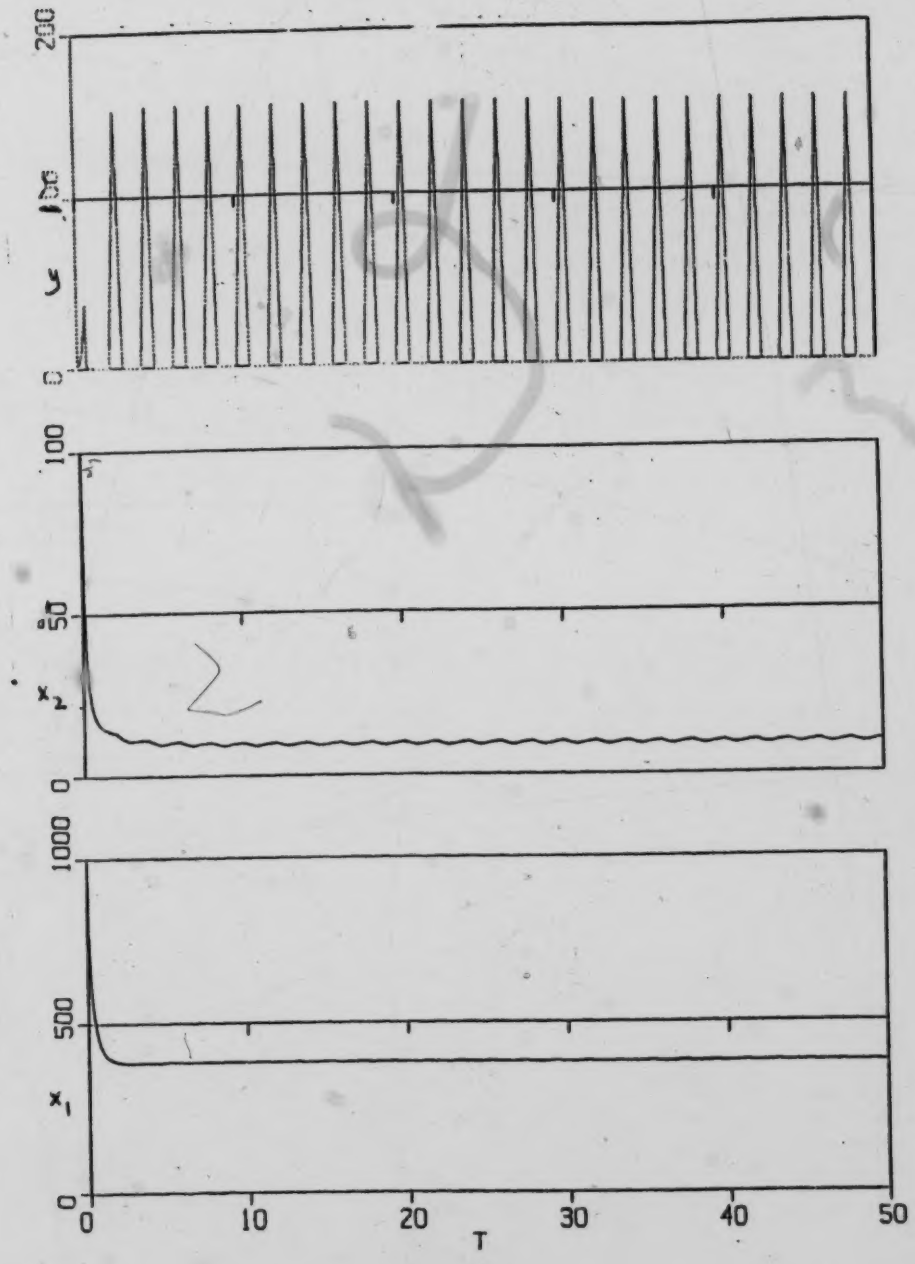

Figure 2.5

Periodic chemotheraphy input with Michaelis-Menton uptake.
Constants, initial conditions and $f(t)$ given in text.

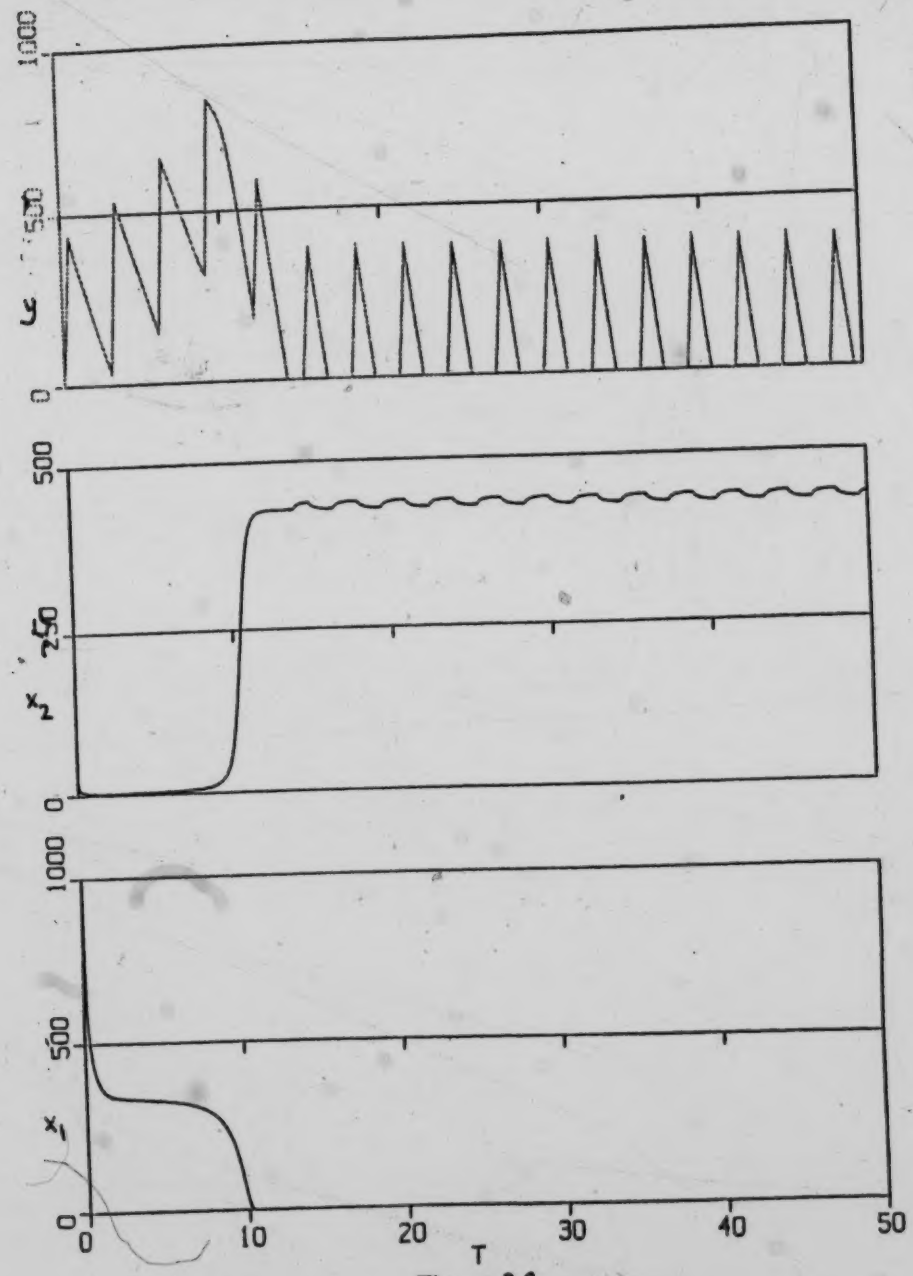

Figure 2.6

Periodic chemotherapy input with Michaelis-Menten uptake.
Normal cells driven to extinction.
Constants, initial conditions and $f(t)$ given in text.

Example 6. All constants and $f(t)$ are as in Example 5, except for $x_{20} = 14$. Now x_1 approaches a steady state with the cancer cells going extinct. Note the periodic accumulation of chemotherapy agent (see Fig. 2.7).

2.8. Conclusions

In this paper we have proposed a model of chemotheraphy on cancer cells in competition with normal cells, consisting of three interacting ordinary differential equations. We have analyzed the solutions for various types of chemostat inputs including a finite number of constant inputs, a sustained constant input, and sustained periodic inputs.

Our models show that the following scenarios are possible: cancer causes the normal cells to go extinct (presumably resulting in death); cancer cells go extinct; cancer cells kept at a low level; all cells approach a steady state which is high for the cancer cells; all cells and chemotherapy approach periodic oscillations.

An interesting case is shown in comparing Examples 5 and 6. The examples are idential except for the cancer cell starting values. In the latter case, with $x_{20} = 14$, the cancer is driven to extinction whereas in the former the cancer drives the normal cells to extinction with $x_{20} = 15$. This shows that outcomes could be very sensitive on cancer values immediately before treatment, which means early detection and treatment may be instrumental to survival.

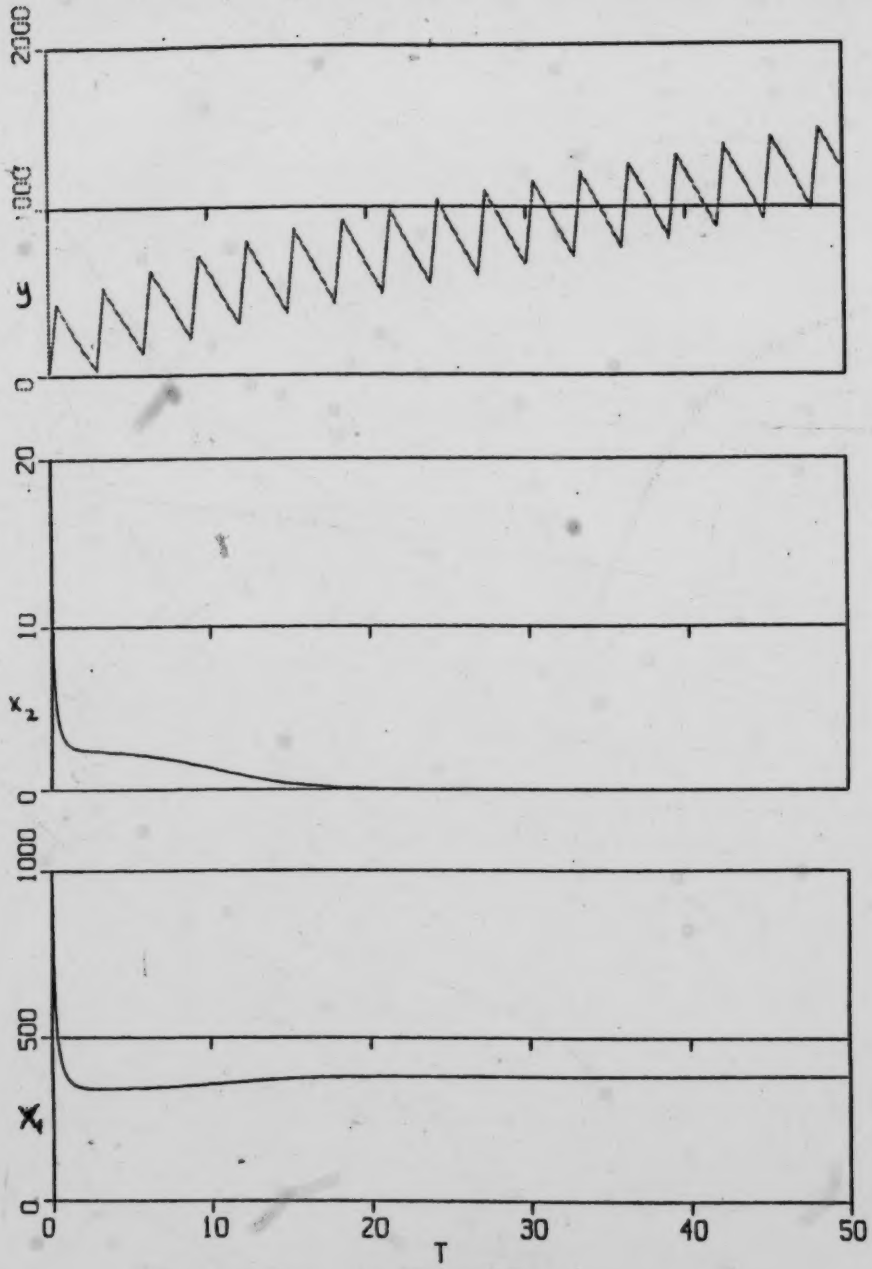

Figure 2.7

Periodic chemotherapy input with Michaelis-Menton uptake.
Cancer cells driven to extinction.
Constants, initial conditions and $f(t)$ given in text.

2.9. Appendix

In this appendix we indicate the process leading to a bifurcation of the planar periodic solution $(\varphi_1(t), 0, \psi(t))$ of system (2.33) into an interior periodic solution. The idea is to set up a period time map and use the implicit function theorem to establish a second periodic solution.

Step 1. First we define $\widehat{B}_2(x_2)$ and the constant b by $B_2(x_2) = b\widehat{B}_2(x_2)$. b will be our bifurcation parameter. Under the assumption that $(\varphi_1(t), 0, \psi(t))^T$ is a periodic solution of period ω of (2.33), we define

$$g(t,b) = b\widehat{B}_2'(0) - D_2'(0) - \varphi_1(t)q_2(\varphi_1(t), 0) - p_2'(0)u(\psi(t)) \tag{2.38}$$

and

$$\Phi(t) = (\varphi_1(t), 0, \psi(t))^T. \tag{2.39}$$

Then computing the variational matrix M about $\Phi(t)$, we get

$$M(\Phi(t)) =$$

$$\begin{bmatrix} b\widehat{B}_1'(\varphi_1(t)) - D_1'(\varphi_1(t)) - p_1'(\varphi_1(t))u(\psi(t)) & -\varphi(t)q_1(\varphi_1(t), 0) & -p_1(\varphi_1(t))u'(\psi(t)) \\ 0 & g(t,b) & 0 \\ -\eta_1 p_1'(\varphi_1(t))u(\psi(t)) & -\eta_2 p_2'(0)u(\psi(t)) & -[\gamma + \eta_1 p_1(\varphi_1(t))]u'(\psi(t)) \end{bmatrix}.$$

From $M(\Phi(t))$ we see that if $\int_0^\omega g(t,b)dt < 0$ (resp. > 0) then there is local stability (resp. instability) in the x_2 direction. Bifurcation will occur if by

changing b, the system loses stability.

Step 2. We now move the periodic solution $\Phi(t)$ to the origin by a change of variables and then separate off the linear part of the resulting system.

Let

$$w_1 = x_1 - \varphi_1(t), \quad w_2 = x_2, \quad z = y - \psi(t). \tag{2.40}$$

This results in the system

$$\begin{aligned}
\dot{w}_1 &= B_1(w_1 + \varphi_1(t)) - B_1(\varphi_1(t)) - D_1(w_1 + \varphi_1(t)) + D_1(\varphi_1(t)) \\
&\quad - (w_1 + \varphi_1(t))w_2 q_1(w_1 + \varphi_1(t), w_2) \\
&\quad - p_1(w_1 + \varphi_1(t))u(z + \psi(t)) + p_1(\varphi_1(t))u(\psi(t)) \\
&\equiv \Theta_1(t, w_1, w_2, z, b).
\end{aligned} \tag{2.41}$$

$$\begin{aligned}
\dot{w}_2 &= b\widehat{B}_2(w_2) - D_2(w_2) - (w_1 + \varphi_1(t))w_2 q_2(w_1 + \varphi_1(t), w_2) \\
&\quad - p_2(w_2)u(z + \psi(t)) \\
&\equiv \Theta_2(t, w_1, w_2, z, b)
\end{aligned}$$

$$\begin{aligned}
\dot{z} &= -[\gamma + \eta_1 p_1(w_1 + \varphi_1(t)) + \eta_2 p_2(w_2)]u(z + \psi(t)) \\
&\quad + [\gamma + \nu_1 p_1 \varphi_1(t)]u(\psi(t)) \\
&\equiv \Theta_3(t, w_1, w_2, z, b).
\end{aligned}$$

Note that $\Theta_i(t,0,0,0,b) = 0$ and so $E_0 = (0,0,0)^T$ is a periodic solution of system (2.40).

Let $A(t) = M(\Phi(t)) = (a_{ij}(t))$, let $u = (w_1, w_2, z)^T$, $\Theta = (\Theta_1, \Theta_2, \Theta_3)^T$ and $N(t,u,b) = \Theta(t, w_1, w_2, z, b) - A(t)u$. Then $N(t,0,b) = \Theta(t,0,0,0,b) - 0 = 0$, $\frac{\partial N}{\partial u}(t,0,b) = A(t) - A(t) = 0$. Hence system (2.41) can be written as

$$\dot{u} = A(t)u + N(t,u,b) \tag{2.42}$$

where $N(t,u,b)$ is nonlinear in u.

Step 3. First note that by a result of Poincaré (see [8]) if the system

$$\dot{u} = A(t)u \tag{2.43}$$

has no nontrivial solutions of period ω, then system (2.42) has a unique periodic solution of period ω, and since E_0 is such a solution, there can be no bifurcation. Hence we assume

(H): System (2.43) has one or more non-trivial periodic solutions of period ω.

In preparation for bifurcation using the implicit function theorem, note that $g(t,0) < \infty$ while $\lim_{b\to\infty} g(t,b) > 0$. Further, $\frac{\partial g(t,b)}{\partial b} = \widehat{B}'(0) > 0$. Hence there exists a unique $b_0 > 0$ such that $\int_0^\omega g(t,b_0)dt = 0$.

Finally we define ε by

$$\varepsilon = b - b_0.$$

Step 4. Let $u(t,\xi,\varepsilon)$ be that solution of (2.42) such that $u(0,\xi,\varepsilon)=\xi$. Note that $u(t,0,0)=0$. Define the vector function $F(\xi,\varepsilon)$ by

$$F(\xi,\varepsilon)=u(\omega,\xi,\varepsilon)-\xi. \tag{2.44}$$

If the equation $F(\xi,\varepsilon)=0$ can be solved for ξ as a function of ε such that $\lim_{\varepsilon\to 0}\xi(\varepsilon)=0$, then we will have found a periodic solution.

Now $F(0,0)=u(\omega,0,0)=0$. $F_\xi(0,0)=u_\xi(\omega,0,0)-I$. But $u_\xi(t,\xi,\varepsilon)$ satisfies

$$\dot{u}_\xi=A(t)u_\xi+N_u(t,u,b)u_\xi,\quad u_\xi(0,\xi,\varepsilon)=I.$$

Hence at $\xi=0$, $\varepsilon=0$, we get

$$\dot{u}_\xi=A(t)u_\xi+N_u(t,0,b_0)u_\xi\quad u_\xi(0,0,0)=I,$$

or

$$\dot{u}_\xi=A(t)u_\xi,\quad u_\xi(0,0,0)=I$$

since N is nonlinear in u.

Let $\Psi(t)$ be that fundamental matrix solution of (2.43) such that $\Psi(0)=I$. Then

$$F_\xi(0,0)=\Psi(\omega)-I,$$

and by hypothesis (H), we obtain that $\det F_\xi(0,0)=0$. Hence we are in the required singular case of the implicit function theorem.

We will also need to compute $F_\varepsilon(0,0)$. $F_\varepsilon(\xi,\varepsilon) = u_\varepsilon(\omega,\xi,\varepsilon)$. Now $u_\varepsilon(t,\xi,\varepsilon)$ satisfies

$$\dot{u}_\varepsilon = A(t)u_\varepsilon + N_u(t,u,b)u_\varepsilon + N_b(t,u,b), \quad u_\varepsilon(0,\xi,\xi) = 0.$$

At $\xi = \varepsilon = 0$, $u_\varepsilon(t,0,0)$ satisfies

$$\dot{u}_\varepsilon = A(t)u_\varepsilon + N_b(t,0,b_0), \quad u_\varepsilon(0,0,0) = 0.$$

Hence

$$u_\varepsilon(t,0,0) = \Psi(t)\int_0^t \Psi(s)^{-1}N_b(s,0,b_0)ds \tag{2.45}$$

and so

$$F_\varepsilon(0,0) = \Psi(\omega)\int_0^\omega \Psi(s)^{-1}N_b(s,0,b_0)ds.$$

Note that $N_b(s,0,b_0) = (0,\widehat{B}_2'(0),0)^T$ is a constant vector.

Step 5. Here we discuss the first of three generic cases.

Case (i): $F_\xi(0,0) = 0, \quad F_\varepsilon(0,0) = 0.$

In this case, $F(\xi,\varepsilon)$ begins with quadratic or higher terms. We begin by defining the vector η by

$$\xi = \eta\varepsilon \tag{2.46}$$

and setting

$$G(\eta,\varepsilon) = \begin{cases} \varepsilon^{-2}F(\eta\varepsilon,\varepsilon), & \varepsilon \neq 0 \\ \frac{1}{2}F_{\xi\xi}(0,0)\eta^2 + F_{\xi\varepsilon}(0,0)\eta + \frac{1}{2}F_{\varepsilon\varepsilon}(0,0), & \varepsilon = 0. \end{cases}$$

In order to solve $G(\eta, \varepsilon) = 0$ for η as a function of ε, we first must find a vector η_0 such that $G(\eta_0, 0) = 0$, i.e.

$$\frac{1}{2} F_{\xi\xi}(0,0)\eta_0^2 + F_{\xi\varepsilon}(0,0)\eta_0 + \frac{1}{2} F_{\varepsilon\varepsilon}(0,0) = 0. \tag{2.47}$$

Computing the second derivative, in a similar manner as the above, we get

$$\begin{aligned} F_{\xi\xi}(0,0) &= \Psi(\omega) \int_0^\omega \Psi(s)^{-1} N_{uu}(s,0,b_0) \Psi^{-1}(s)^2 ds \\ F_{\xi\varepsilon}(0,0) &= \Psi(\omega) \int_0^\omega \Psi^{-1}(s) N_{uu}(s,0,b_0) u_\xi(s,0,0) u_\varepsilon(s,0,0) ds \\ F_{\varepsilon\varepsilon}(0,0) &= \Psi(\omega) \int_0^\omega \Psi^{-1}(s) N_{uu}(s,0,b_0) u_\varepsilon(s,0,0)^2 ds. \end{aligned} \tag{2.48}$$

Note that $F_{\varepsilon\varepsilon}$ is a vector, $F_{\xi\varepsilon}$ is a 3×3 matrix and $F_{\xi\xi}$ is a $3 \times 3 \times 3$ tensor. Hence (2.48) is equivalent to solving three quadratic equations in three unknowns (the components of η). It can have up to nine distinct solutions.

If (2.48) has no real solution then ξ cannot be solved for ε. Hence we make the following assumption.

(H2): Equation (2.48) has at least one real distinct solution η_0.

With assumption (H2) we get that $G(\eta_0, 0) = 0$. Now we compute $G_\eta(\eta_0, 0)$ and $G_\varepsilon(\eta_0, 0)$.

$$G_\eta(\eta_0, 0) = \lim_{\varepsilon \to 0} \frac{F_\xi(\eta_0 \varepsilon, \varepsilon)}{\varepsilon} = F_{\xi\xi}(0,0)\eta_0 + F_{\xi\varepsilon}(0,0)$$

$$G_\varepsilon(\eta_0, 0) = \lim_{\varepsilon \to 0} \frac{d}{d\varepsilon} \left(\frac{F(\eta\varepsilon, \varepsilon)}{\varepsilon^2} \right)$$

$$= \frac{1}{3} \lim_{\varepsilon \to 0} \frac{F_\xi(\eta_0\varepsilon, \varepsilon)\eta_0 + F_\varepsilon(\eta_0\varepsilon, \varepsilon)}{\varepsilon^2}$$

which in light of (H2) gives

$$G_\varepsilon(\eta_0, 0) = \frac{1}{3} F_{\xi\xi\xi}(0,0)\eta_0^3 + F_{\xi\xi\varepsilon}(0,0)\eta_0^2$$
$$+ F_{\xi\varepsilon\varepsilon}(0,0)\eta_0 + \frac{1}{3}F_{\varepsilon\varepsilon\varepsilon}(0,0),$$

where these derivatives are computed similar to the second derivatives.

(H3): Hence if $\det G_\eta(\eta_0, 0) \neq 0$, we can solve for η as a function of ε, i.e.

$$\eta = \eta_0 - G_\eta(\eta_0, 0)^{-1} G_\varepsilon(\eta_0, 0)\varepsilon + o(\varepsilon),$$

or

$$\xi = \eta_0\varepsilon - G_\eta(\eta_0, 0)^{-1} G_\varepsilon(\eta_0, 0)\varepsilon^2 + o(\varepsilon^2). \tag{2.49}$$

Step 6. Since $u(t, \xi, \varepsilon)$ is a periodic perturbation of $\Phi(t)$, then $w_1(t, \xi, \varepsilon)$ and $z(t, \xi, \varepsilon)$ are positive for ε sufficiently small.

With respect to w_2, we note that $u(t, \xi, \varepsilon)$ can be written as

$$u(t, \xi, \varepsilon) = u(t, 0, 0) + u_\xi(t, 0, 0)\xi + u_\varepsilon(t, 0, 0)\varepsilon + \text{H.O.T.}$$
$$= \Psi(t)[\eta_0 + \int_0^t \Psi(s)^{-1}(0, \widehat{B}_2'(0), 0)^T ds]\varepsilon + o(\varepsilon)$$
$$= \chi(t)\varepsilon + o(\varepsilon).$$

Hence for $w_2 > 0$ for $\varepsilon > 0$, we require that the middle component of $\chi(t)$ be positive, $0 \le t \le \omega$.

Step 7.

Case (ii): $F_\xi(0,0) = 0, \quad F_\varepsilon(0,0) \neq 0$. In this case we assume that there exists $n \ge 2$ such that $\det\left(F_{\xi^n}(0,0)\right) \neq 0$. To illustrate the technique, assume $n = 2$.

First we set $\varepsilon = \tau^2$ and

$$H(\xi, \tau) = F(\xi, \tau^2). \tag{2.50}$$

Then as before, we set $\xi = \eta\varepsilon$ and define

$$J(\eta, \varepsilon) = \begin{cases} H(\eta\varepsilon, \tau)\varepsilon^{-2}, & \varepsilon \neq 0 \\ \frac{1}{2} H_{\xi\xi}(0,0)\eta^2 + H_{\xi\tau}(0,0)\eta + \frac{1}{2} H_{\tau\tau}(0,0), & \varepsilon = 0, \end{cases} \tag{2.51}$$

where here

$$\begin{aligned} H_{\xi\xi}(0,0) &= F_{\xi\xi}(0,0) \\ H_{\xi\tau}(0,0) &= 0 \\ H_{\tau\tau}(0,0) &= 2F_\varepsilon(0,0). \end{aligned} \tag{2.52}$$

Hence as in Step 5, one requires a real distinct solution to the system

$$F_{\xi\xi}(0,0)\eta^2 + 2F_\varepsilon(0,0) = 0. \tag{2.53}$$

If such a real solution, η_0, does not exist, then instead of $\varepsilon = \tau^2$, one can try $\varepsilon = -\tau^2$ and that may work, otherwise no bifurcation occurs.

If η_0 exists (in which case there are two or no branches for ξ as a function of ε) the rest proceeds as in Steps 5 and 6.

Step 8. Case (iii), $\det\left(F_\xi(0,0)\right) = 0$, $F_\xi(0,0) \neq 0$. This case is somewhat complicated. First by a linear change of variables, we assume that $F_\xi(0,0)$ is in Jordan canonical form with all zero eigenvalues on the upper left on the diagonal. We then define all rows which consist only of zero to be the *singular rows* and all such columns to be the *exceptional columns*. Then if $F(\xi,\varepsilon)$ is broken into singular and nonsingular parts, F_s and $\widetilde{F}$ respectively, and ξ into exceptional and nonexceptional components, ξ_e and $\widehat{\xi}$ respectively, one can see that $\det\left(\widetilde{F}_{\widehat{\xi}}(0,0)\right) \neq 0$.

Hence $\widetilde{F}(\xi,\varepsilon)$ can be solved for $\widehat{\xi}$ as a function of ξ_e and ε. We then substitute into $F_s(\xi,\varepsilon)$, giving a system of the form $F_s(\xi_e,\varepsilon) = 0$, where now $F_{s\xi_e}(0,0) \equiv 0$. Then we proceed as in Steps 5 and 6, or Step 7. See [8] for complete details of this technique.

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CHAPTER 3

A MATHEMATICAL MODEL OF CANCER TREATMENT BY IMMUNOTHERAPY

In this chapter, a detailed mathematical study of cancer immunotherapy will be presented. In the succeeding sections, we will discuss the general principles of cancer immunotherapy §3.1, §3.2, the model equations and hypotheses §3.3, and mathematical analyses of the model equations with regard to dissipativity, boundedness of solutions, invariance of non-negativity §3.4, nature of equilibria §3.5, persistence, extinction and global stability §3.6 and §3.7. In §3.8 we do a bifurcation analysis and in §3.9 we examine a criteria for total cure.

3.1. The Immune System and Cancer

When cancer cells proliferate to a detectable threshold number in a given physiological space of the human anatomy, the body's own natural immune system is triggered into a search-and-destroy mode. The spontaneous immune response is possible if the cancer cells possess distinctive surface markers called Tumor Specific Antigens. Tumor cells which possess such antigens are called immunogenic cancers, [14,3,19,29,30]. The immune response against cancer cells can be categorized into two types: the *cellular* and the *humoral* immune response.

The cellular natural immune response is provided by (i) Lymphocytes (ii) Lym-

phokines/cytokines and (iii) Antigen-presenting cells.

The effector Lymphocytes which are involved in anti-cancer mechanisms are T cells, NK cells, LAK cells and K cells. The Lymphokines or cytokines are biological response modifiers or growth-stimulating substances biosynthesized by certain immune cells. These include the interleukins and the interferons. In particular, interleukin-2 (IL-2) is biosynthesized by an antigen-sensitized subset of the T-cells called Helper T cells. Interleukin-2 is responsible for stimulating antigen sensitized NK cells, cytotoxic T-cells and LAK cells to develop into mature anti-cancer effector lymphocytes and also provides the growth stimulus for these lymphocytes to proliferate into a high enough cell number capable of mounting an effective attack against the cancer cells. The Antigen Presenting Cells include Macrophages and Dendritic cells. These cells are responsible for presenting cancer antigens to the T cells such as to trigger the immune response. The detailed description of the morphology and roles of the lymphocytes, lymphokines and antigen-presenting cells can be obtained from the following references: [19,29,30].

The Humoral Immune response to cancer is provided by

(i) B-lymphocytes and

(ii) Immunoglobulins/Antibodies.

There exists a mechanism in which both cellular and humoral responses cooperate in providing an anti-cancer activity. This mechanism is called Antibody Dependent Cancer Cell Destruction: cf. [3,19,30], and it involves K and NK cells as well as interleukin-2 and immunoglobulin-G.

The cellular response is the most prolific against most cancers and usually the first line of action. The basic steps involved in a cellular immune response are listed as follows:

s_1 : Cancer cells develop in a given physiological space of the human anatomy. The cancer cells could be immunogenic or non-immunogenic.

s_2 : The cancer cells subvent the immuno-surveillance activity provided by NK cells (which can kill cancer cells whether immunogenic or not).

s_3 : The cancer cells proliferate above the subclinical threshold of 10^3 cells and reach 10^9 cells which is the x-ray detectable threshold. Some cancer cells might have metastasized to other physiological regions of the human anatomy.

s_4 : The antigen presenting cells, particularly macrophages, encounter the cancer cells. They internalize the cancer cells, dissolve them into fragments called epitopes. These epitopes bear the cancer associated antigens. The macrophages then exhibit the cancer antigens on their surfaces and circulate into the vicinity of T cells (particularly helper T cells) and mechanistically present these cancer antigens to them, cf. [19,30].

s_5 : The antigen-sensitized helper T cells then release the immuno-stimulatory growth substance called interleukin-2. This lymphokine, IL-2, then stimulates the cancer killing subset of the T cells called the cytotoxic T cells, to mature and proliferate. In particular, the IL-2 also enhances the proliferation of NK and LAK cells.

s_6 : The activated lymphocytes (LAK, T, NK cells) then engage in a search-and-destroy anti-cancer activity.

The process of natural immune attack against immunogenic cancers is not always sustainable nor eventually successful and can always be terminated or downgraded due to one or all of the following reasons: cf. [20,29,30,33].

r_1 : The initial numbers of the cancer-killing lymphocytes at the time of tumor diagnosis or initiation of therapy are insignificant and easily overwhelmed by the rapidly proliferating tumor cells.

r_2 : The cancer cells eventually evade the immune recognition mechanism by shedding, altering or re-distributing its surface tumor associated antigens, cf. [29,30]. The 'stealth' tumor then becomes non-immunogenic.

r_3 : Some of the shedded tumor antigens and receptors bind to form circulating immune complexes which interact destructively with the surface receptors on the cancer cells and thereby effectively block the cancer-killing lymphocytes from getting access to the cancer cells [33].

r_4 : Cancer cells release inhibitory substances which effectively reduce the therapeutic efficacy of the cancer-killing lymphocytes, cf. [29].

In view of the processes $r_1 - r_4$ it is observed by clinical investigators and medical oncologists that the natural immune system cannot provide a sustained and therapeutically successful anti-cancer attack, cf. [3,29,30].

Further research by clinical oncologists including those at the National Cancer Institute led to the development of several techniques and methodologies to enhance the natural immune response against cancer. Some of these novel approaches include, cf. [3,10,13,14,27,28]

(i) non-specific cancer immunotherapy

(ii) specific passive cancer immunotherapy (adoptive cancer immunotherapy)

(iii) specific active cancer immunotherapy

(iv) gene therapy of cancer

(v) monoclonal antibody mediated anti-tumor immunization of host via induction of idiotype-anti-idiotypic immune network.

In the next subsection we shall present an elaborate clinical description of Adoptive Cancer Immunotherapy (ACI) and construct a plausible mathematical model depicting the procedure. The choice of ACI is based on its current status as the most clinically successful and promising during clinical trials and applications to advanced cancers [2,11,12,15,16,25].

3.2. Clinical Principles of Adoptive Cancer Immunotherapy

Adoptive cancer immunotherapy is a relatively new immunotherapeutic modality for treating advanced and metastatically disseminated human solid tumors, cf. [11,12,22,24,25,26,28]. It involves the use of tumor-killing lymphocytes and

lymphokines such as natural or cloned interleukin-2 (n-IL-2, or r-IL-2), natural killer (NK) cells, tumor infiltrating lymphocytes (TIL), interferon $-\gamma$ activated killer monocytes (AKM) and lymphokine activated killer cells (LAK).

The mathematical models will be based on LAK ACI using interleukin-2. The use of LAK and IL-2 therapy has been given prominence due to the work of S.A. Rosenberg and colleagues at the National Cancer Institute, cf. [24,25,26,28]. In LAK ACI, the LAK precursor mononuclear lympthocytes are clinically extracted from the cancer patients' body by a process called cytapheresis. The LAK cells are then incubated (outside the patient's body for at least 48 hours) using high dose interleukin-2. Two phenotypes of LAK cells are called NK-LAK or A-LAK and T-LAK depending on their precursors are produced. The NK-LAK cells have been used for adoptive immunotherapy of metastatic cancers, cf. [11,12,22]. T-LAK cells have also been used in adoptive immunotherapy of ovarian cancer and malignant brain tumors [15,22]. In LAK ACI, the LAK cells are incubated with high dose IL-2 until the number of LAK cells is of the order of $10^7 - 10^8$ cells. They are then re-transfused by intravenous injection infusion into the patient in addition to continuous infusion of IL-2 in the order of 10^5 units/m^2/day or 10^6 units/kg/day of rIL-2, cf. [22,28].

3.3. The Mathematical Model of ACI for Solid Tumors

In this subsection, the mathematical model for ACI will be presented.

Notation:

x_1 : The concentration of normal/non-cancer cells in the physiologic space or organ of the human anatomy where cancer cells are localized.

x_2 : The concentration of cancer cells in a given physiologic space or organ of the human anatomy.

w : The concentration of cancer-killing lymphocyte binding sites such as LAK cells in the neighborhood of the cancer cells and normal cells.

z : The concentration of lymphokine (eg. IL-2) in the neighborhood of the cancer cells and normal cells.

Q_1 : The rate of external (adoptive) intravenous re-infusion of lymphocyte (LAK cells) into the cancer patient.

Q_2 : The rate of external (adoptive) intravenous re-infusion of lymphokines (IL-2) into the cancer patient.

S_1 : The rate of internal production of lymphocytes (LAK cells).

S_2 : The rate of internal production of lymphokines (IL-2).

The model equations are as follows:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2)$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - h(x_2, w)$$

$$\dot{w} = S_1 + Q_1 - \alpha_1 e_1(w) + f(\omega, z) - \beta h(x_2, w)$$

$$\dot{z} = S_2 + Q_2 - \alpha_2 e_2(z) - \eta f(w, z)$$

$$x_i(t_0) = x_{i0} \geq 0, \qquad i = 1, 2$$

$$w(t_0) = w_0 \geq 0$$

$$z(t_0) = z_0 \geq 0 \tag{3.0}$$

where

$f(w, z)$ is the rate of lymphocyte (LAK) proliferation due to induction by lymphokine (IL-2),

$h(x_2, w)$ is the rate of cancer cell destruction by (cancer killing) lymphocytes,

$e_1(w)$, $e_2(z)$ are the rates of degradation or elimination of lymphocytes (LAK) or lymphokine (IL-2) respectively,

η, β are constants depicting binding stoichiometry,

α_i are elimination coefficients.

We shall assume that $Q_i \gg S_i$ are such that the process relies solely on the rate of adoptive transfer of LAK cells and IL-2. Then S_i is negligible and will subsequently be omitted. Furthermore, the toxicity to normal cells is assumed to be minimal and hence not represented in the models. This can be achieved in practice by use of low dose IL-2, cf. [2,22,23].

Thus the final form of the model equations are:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2)$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - h(x_2, w)$$

$$\dot{w} = Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w)$$

$$\dot{z} = Q_2 - \alpha_2 e_2(z) - \eta f(w, z)$$

$$x_i(t_0) = x_{i0} \geq 0 \quad \text{for} \quad i = 1, 2$$

$$w(t_0) = w_0 \geq 0, \quad z(t_0) = z_0 \geq 0. \tag{3.0a}$$

The following additional hypotheses are assumed to hold:

$\mathbb{P}_1$: The initial conditions are such that $(x_{10}, x_{20}, w_0, z_0) \in \overline{\mathbb{R}}^4_+$.

$\mathbb{P}_2$: (a) $f(w, z) \in C^1(\mathbb{R}_+ \times \mathbb{R}_+, \mathbb{R}_+)$

(b) $f_w(w, z) > 0, \quad w > 0, \quad z > 0$

(c) $f_z(w, z) > 0, \quad w > 0, \quad z > 0$

(d) $f(0, z) = 0, \quad f(w, 0) = 0.$

$\mathbb{P}_3$: (a) $h(x_2, w) \in C^1(\mathbb{R}_+ \times \mathbb{R}_+, \mathbb{R}_+)$

(b) $h_{x_2}(x_2, w) > 0, \quad x_2 > 0, \quad w > 0$

(c) $h_w(x_2, w) > 0, \quad x_2 > 0, \quad w > 0$

(d) $h_w(0, w) = 0, \quad w > 0$

(e) $h_{x_2}(0, w) \neq 0, \quad w > 0$

(f) $h(0, w) = 0, \quad h(x_2, 0) = 0.$

(Some plausible expressions for $h(x_2, w)$ include: (i) $\frac{a_1 x_2}{a_2 \cdot x_2} \cdot \frac{b_1 w}{b_2 + w}$ and (ii) $\frac{c_1 x_2 w}{c_2 + c_3 x_2 + c_4 w}$)

$\mathbb{P}_4$: (a) $e_i \in C^1(\mathbb{R}_+, \mathbb{R})$

(b) $e_i(0) = 0$

(c) $e'(w) > 0, \quad w > 0$

(d) $e'(z) > 0, \quad z > 0.$

3.4. Boundedness, Invariance of Non-Negativity, and Dissipativity

In this subsection, we shall show that the model equations are bounded, positively (non-negatively) invariant with respect to a region in $\mathbb{R}^4_+$, and dissipative.

Theorem 3.0. *Let* $\mathbb{B}$ *be the region defined as*

$$\mathbb{B} = \left\{ (x_1, x_2, w, z) \in \mathbb{R}^4_+ \;\middle|\; \begin{array}{l} 0 \le x_1 \le K_1, \quad 0 \le x_2 \le K_2, \\ 0 \le w \le -\frac{Q_1}{\delta_1}, \text{ where } \delta_1 < 0 \\ 0 \le z \le \frac{Q_2}{\delta_2}, \quad \text{where } \delta_2 > 0 \end{array} \right\}. \tag{3.1}$$

Then

(i) $\mathbb{B}$ *is positively invariant.*

(ii) *All solutions of* (3.0) *with initial values in* $\overline{\mathbb{R}^4_+}$ *are eventually uniformly bounded and are attracted into the region* $\mathbb{B}$.

(iii) *The system* (3.0) *is dissipative.*

Proof. Let $x_{10} > 0$. Consider

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2)$$

$$\Longrightarrow \dot{x}_1 < B_1(x_1) - D_1(x_1).$$

But there exists K_1 such that $B_1(K_1) = D_1(K_1)$ by hypothesis. Thus

$$x_1(t) \leq \max(K_1, x_{10}).$$

Note that $\dot{x}_1 < 0$ for $x_1 > K$ and hence

$$\limsup_{t \to \infty} x_1(t) \leq K_1.$$

For

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - h(x_2, w),$$

a similar analysis gives

$$x_2(t) \leq \max(K_2, x_{20})$$

and

$$\limsup_{t \to \infty} x_2(t) \leq K_2.$$

Now consider

$$\dot{w} = Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w)$$

$$\Longrightarrow \dot{w} < Q_1 + f(w, z) - \alpha_1 e_1(w)$$

$$\Longrightarrow \dot{w} < Q_1 + w \max_{w,z \in \mathbb{B}} \widetilde{f}(w,z) - w\alpha_1 \min_{w \in \mathbb{B}} \widetilde{e}_1(w)$$

where

$$f(w,z) = w\widetilde{f}(w,z)$$

$$e_1(w) = w\widetilde{e}_1(w).$$

Now

$$\dot{w} < Q_1 + w \max_{w,z \in \mathbb{B}} \left\{ \max_{w,z \in \mathbb{B}} \widetilde{f}(w,z) - \alpha_1 \min_{w \in \mathbb{B}} \widetilde{e}_1(w) \right\}.$$

Let

$$\delta_1 = \max_{w,z \in \mathbb{B}} \left\{ \max_{w,z \in \mathbb{B}} \widetilde{f}(w,z) - \alpha_1 \min_{w \in \mathbb{B}} \widetilde{e}_1(w) \right\}. \tag{3.2}$$

We shall henceforth assume that

$$\max_{w,z \in \mathbb{B}} \widetilde{f}(w,z) < \alpha_1 \min_{w \in \mathbb{B}} \widetilde{e}_1(w)$$

and consequently $\delta_1 < 0$. Then $w \leq -\frac{Q_1}{\delta_1} + w_0 e^{\delta_1 t}$. Thus

$$w \leq \max\left(-\frac{Q_1}{\delta_1}, w_0\right)$$

$$\Longrightarrow \limsup_{t \to \infty} w \leq -\frac{Q_1}{\delta_1}, \quad \delta_1 < 0, \quad w_0 \geq 0. \tag{3.3}$$

Similarly we consider the z equation:

$$\dot{z} = Q_2 - \alpha_2 e_2(z) - \eta f(w,z)$$

$$\Longrightarrow \dot{z} < Q_2 - \alpha_2 e_2(z)$$

$$< Q_2 - \alpha_2 z \cdot \min_{z \in \mathbb{B}} \widetilde{e}_2(z)$$

where $e_2(z) = z \cdot \tilde{e}_2(z)$.

We shall henceforth assume that

$$\delta_2 = \alpha_2 \min_{z \in \mathbb{B}} \tilde{e}_2(z) > 0. \tag{3.4}$$

Then $z \leq \frac{Q_2}{\delta_2} + z_0 e^{-\delta_2 t}$. Thus $z \leq \max(\frac{Q_2}{\delta_2}, z_0)$ and

$$\limsup_{t \to \infty} z \leq \frac{Q_2}{\delta_2}. \tag{3.5}$$

□

3.5. The Equilibria: Existence and Local Stability

The equilibria of system (3.0) are obtained by solving the system of isocline equations

$$\begin{aligned} B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) &= 0 \\ B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) &= 0 \\ Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w) &= 0 \\ Q_2 - \alpha_2 e_2(z) - \eta f(w, z) &= 0 \end{aligned} \tag{3.6}$$

subject to the hypothesis A1 and $\mathbb{P}_1 - \mathbb{P}_6$.

The possible equilibria are of the form:

(i) $E_0(0, 0, \overset{\circ}{w}, \overset{\circ}{z})$

(ii) $E_1(\overline{x}_1, 0, \overline{w}, \overline{z})$

(iii) $E_2(0, \widehat{x}_2, \widehat{w}, \widehat{z})$

(iv) $E_3(x_1^*, x_2^*, w^*, z^*)$. (3.7)

The existence and local stability of the prospective equilibria are analysed as follows:

Existence and local stability of $E_0(0, 0, \dot{w}, \dot{z})$

The system of equations (3.0) is restricted to $\overline{\mathbb{R}}^+_{wz}$. This leads to the system

$$\begin{cases} \dot{w} = Q_1 + f(w,z) - \alpha_1 e_1(w) \\ \dot{z} = Q_2 - \alpha_2 e_2(z) - \eta f(w,z) \\ w(0) = w_0 \geq 0, \quad z(0) = z_0 \geq 0. \end{cases} \tag{3.8}$$

Theorem 3.1. *Let*

$$L_1 = \max_{w,z \in \mathbb{B}} f(w,z) > 0$$

$$L_2 = \min_{w,z \in \mathbb{B}} \left[\alpha_1 \min_{w \in \mathbb{B}} \widetilde{e}_1(w), \alpha_2 \min_{z \in \mathbb{B}} \widetilde{e}_2(z) \right] > 0. \tag{3.9}$$

Then

$$(w+z) \leq \frac{Q_1 + Q_2 - (\eta - 1)L_1}{L_2} + (w_0 + z_0)e^{-L_2 t}$$

and

$$\limsup_{t \to \infty} (w+z) \leq \frac{Q_1 + Q_2 - (\eta - 1)L_1}{L_2}. \tag{3.10}$$

Proof. Using the system of equations (3.8) we obtain the differential equation:

$$\begin{aligned}(w+z)' &= Q_1 + Q_2 + f(w,z) - \eta f(w,z) - \alpha_1 e_1(w) - \alpha_2 e_2(z) \\ &\leq Q_1 + Q_2 + (1-\eta)\max_{w,z\in\mathbb{B}} f(w,z) - \alpha_1 w \min_{w\in\mathbb{B}} \widetilde{e}_1(w) - \alpha_2 z \min_{z\in\mathbb{B}} \widetilde{e}_2(z) \\ &\leq Q_1 + Q_2 - (\eta-1)L_1 - (w+z)\min_{w,z\in\mathbb{B}} [\alpha_1 \min_{w\in\mathbb{B}} \widetilde{e}_1(w), \alpha_2 \min_{z\in\mathbb{B}} \widetilde{e}_2(z)]\end{aligned}$$

and

$$(w+z) \leq \frac{Q_1 + Q_2 - (\eta-1)L_1}{L_2} + (w_0+z_0)e^{-L_2 t}$$

and hence

$$\limsup_{t\to\infty} (w+z) \leq \frac{Q_1 + Q_2 - (\eta-1)L_1}{L_2}\,.$$

Lemma 3.0. *Suppose there exists* $(\mathring{w},\mathring{z}) \in \overline{\mathbb{R}}^{+}_{wz}$ *such that*

$$Q_1 - \alpha_1 e_1(\dot{w}) + \frac{1}{\eta}(Q_2 - \alpha_2 e_2(\mathring{z})) = 0$$

as $t \to \infty$. *Then* $E_0(0,0,\mathring{w},\mathring{z})$ *exists.*

Proof. By equating the right side of system (3.8) to zero, we have the two surfaces:

$$\Gamma_1 : Q_1 - \alpha_1 e_1(w) + f(w,z) = 0$$

$$\Gamma_2 : Q_2 - \alpha_2 e_2(z) - \eta f(w,z) = 0.$$

We have shown by Theorem 3.1 that system (3.8) is dissipative under the stated

conditions, of the theorem. Now

$$\alpha_1 e_1(w) - Q_1 = f(w,z)$$

$$\frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(z)\right) = f(w,z).$$

Then

$$\alpha_1 e_1(w) - Q_1 = \frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(z)\right)$$

$$\iff \alpha_1 e_1(w) - Q_1 - \frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(z)\right) = 0$$

$$\iff Q_1 - \alpha_1 e_1(w) + \frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(z)\right) = 0.$$

The lemma now follows immediately.

□

We now discuss the (local) linearized stability of system (3.0) restricted to a neighborhood of the equilibrium $E_0(0,0,\mathring{w},\mathring{z})$.

The Jacobian matrix due to the linearization of (3.0) about an arbitrary equilibrium $E(x_1,x_2,w,z) \in \overline{\mathbb{R}}^4_+$ is given by

$$J_{E(x_1,x_2,w,t)} =$$

$$\begin{pmatrix} B_1'(x_1) - D_1'(x_1) & -x_1 q_1(x_1,x_2) & 0 & 0 \\ -x_2 q_1(x_1,x_2) & -x_1 x_2 q_{1,x_2}(x_1,x_2) & & \\ -x_1 x_2 q_{1,x_1}(x_1,x_2) & & & \\ & B_2'(x_2) - D_2'(x_2) & & \\ -x_2 q_2(x_1,x_2) & -x_1 q_2(x_1,x_2) & -h_w(x_2,w) & 0 \\ -x_1 x_2 q_{2,x_1}(x_1,x_2) & -x_2 x_1 q_{2,x_2}(x_1,x_2) & & \\ & -h_{x_2}(x_2,w) & & \\ 0 & -\beta h_{x_2}(x_2,w) & f_w(w,z) - \beta h_w(x_2,w) & f_z(w,z) \\ & & -\alpha_1 e_1'(w) & \\ 0 & 0 & -\eta f_w(w,z) & -\alpha_2 e_2'(z) \\ & & & -\eta f_z(w,z) \end{pmatrix} \tag{3.11}$$

Using hypotheses A1 and $P_1 - P_6$, the Jacobian matrix due to linearization of (3.0) about the rest point $E_0(0,0,\mathring{w},\mathring{z})$ is given by the expression:

$$J_{E_0(0,0,\mathring{w},\mathring{z})} = \begin{pmatrix} B_1'(0) & 0 & 0 & 0 \\ -D_1'(0) & & & \\ 0 & B_2'(0) - D_2'(0) & 0 & 0 \\ & -h_{x_2}(0,\mathring{w}) & & \\ 0 & -\beta h_{x_2}(0,\mathring{w}) & f_w(\mathring{w},\mathring{z}) & f_z(\mathring{w},\mathring{z}) \\ & & -\alpha_1 e_1'(\mathring{w}) & \\ 0 & 0 & -\eta f_w(\mathring{w},\mathring{z}) & -\alpha_2 e_2'(\mathring{z}) \\ & & & -\eta f_z(\mathring{w},\mathring{z}) \end{pmatrix}. \tag{3.12}$$

Henceforth we let M_{22} define the matrix:

$$M_{22} = \begin{pmatrix} f_w(\mathring{w},\mathring{z}) - \alpha_1 e_1'(\mathring{w}) & f_z(\mathring{w},\mathring{z}) \\ -\eta f_w(\mathring{w},\mathring{z}) & -\alpha_2 e_2'(\mathring{z}) - \eta f_z(\mathring{w},\mathring{z}) \end{pmatrix}. \tag{3.13}$$

The eigenvalues of $J_{E_0(0,0,\mathring{w},\mathring{z})}$ are given by

$$\lambda_1 = B_1'(0) - D_1'(0), \quad \lambda_2 = B_2'(0) - D_2'(0) - h_{x_2}(0, \mathring{w}) \tag{3.14}$$

and the eigenvalues of M_{22} are given by

$$\begin{aligned} \sigma(M_{22}) &= \{\lambda_i | \det(M_{22} - \lambda I) = 0,\ i = 3,4\} \\ &= \{\lambda_i | \lambda^2 - (\text{trace } M_{22})\lambda + \det M_{22} = 0,\ i = 3,4\}. \end{aligned} \tag{3.15}$$

By the Routh-Hurwitz criteria, the eigenvalues of M_{22} have negative real parts, i.e. $\text{Re}\,\sigma(M_{22}) < 0$, i.e. if $-\text{Trace } M_{22} > 0$, and $\det M_{22} > 0$.

Theorem 3.2. *If*

(i) $B_1'(0) - D_1'(0) < 0$

(ii) $B_2'(0) - D_2'(0) - h_{x_2}(0, \mathring{w}) < 0$ *and*

(iii) Trace $M_{22} < 0$ *with* $\det M_{22} > 0$, *then the rest point* $E_0(0, 0, \mathring{w}, \mathring{z})$ *is locally asymptotically stable.*

Proof. The proof is by inspection of the eigenvalues of the Jacobian matrix for $E_0(0, 0, \mathring{w}, \mathring{z})$ and the qualitative theory of differential equations, cf. [5,6,7,8].

Theorem 3.3. *Suppose*

(i) $B_1'(0) - D_1'(0) > 0$

(ii) $B_2'(0) - D_2'(0) - h_{x_2}(0, \mathring{w}) > 0$ *and*

(iii) Trace $M_{22} < 0$ *with* det $M_{22} > 0$.

Then the rest point $E_0(0, 0, \mathring{w}, \mathring{z})$ *is a hyperbolic saddle and is repelling in both* x_1 *and* x_2 *directions locally. In particular, the dimensions of the stable manifold* W^+ *and unstable manifold* W^- *are given respectively by*

$$\text{Dim}\, W^+(E_0(0, 0, \mathring{w}, \mathring{z})) = 2, \quad \text{Dim}\, W^-(E_0(0, 0, \mathring{w}, \mathring{z})) = 2.$$

Proof. This result follows directly from inspection of the eigenvalues of the Jacobian matrix for $E_0(0, 0, \mathring{w}, \mathring{z})$ and examples from Freedman and Mathsen [6].

Remark 3.1. Clinically the rest point $E_0(0, 0, \mathring{w}, \mathring{z})$ is not therapeutically feasible and highly unstable.

Existence and local stability analysis of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$.

Consider system (3.0) restricted to $\overline{\mathbb{R}}^+_{x_1 wz}$ as represented by:

$$\begin{cases} \dot{x}_1 = B_1(x_1) - D_1(x_1) \\ \dot{w} = Q_1 - \alpha_1 e_1(w) + f(w, z) \\ \dot{z} = Q_2 - \alpha_2 e_2(z) - \eta f(w, z) \\ x_1(0) = x_{10} \geq 0, \quad z(0) = z_0 \geq 0, \quad w(0) = w_0 \geq 0. \end{cases} \tag{3.16}$$

The possible equilibria in $\overline{\mathbb{R}^+}_{x_1 wz}$ are $\widetilde{E}_1[0, \overline{w}, \overline{z}]$ and $\widetilde{E}_1[\overline{x}_1, \overline{w}, \overline{z}]$. In particular the existence of $\widetilde{E}_1[\overline{x}_1, \overline{w}, \overline{z}]$ (which will be shown by persistence analysis)

will imply the existence of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$.

Using methods similar to the previous subsection, we can conclude that $\widetilde{E}_1[0, \overline{w}, \overline{z}]$ exists in $\overline{\mathrm{IR}}^+_{x_1 wz}$ if there exists $\overline{w}, \overline{z}$ such that

$$Q_1 - \alpha_1 e_1(\overline{w}) + \frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(\overline{z})\right) = 0.$$

We now linearize system (3.16) in the neighborhood of $\widetilde{E}_1[0, \overline{w}, \overline{z}]$. This procedure leads to the result:

$$\dot{\xi} = DF\big(\widetilde{E}_1(0, \overline{w}, \overline{z})\big)\xi \tag{3.17}$$

where $DF\big(\widetilde{E}_1(0, \overline{w}, \overline{z})\big)$ is the Jacobian matrix of the linearization and given by:

$$DF\big(\widetilde{E}_1(0, \overline{w}, \overline{z})\big) = \begin{bmatrix} B_1'(0) - D_1'(0) & 0 & 0 \\ 0 & f_w(\overline{w}, \overline{z}) - \alpha_1 e_1'(\overline{w}) & f_z(\overline{w}, \overline{z}) \\ 0 & -\eta f_w(\overline{w}, \overline{z}) & -\alpha_2 e_2'(\overline{z}) - \eta f_z(\overline{w}, \overline{z}) \end{bmatrix}. \tag{3.18}$$

The eigenvalues of $DF\big(\widetilde{E}_1(0, \overline{w}, \overline{z})\big)$ are given by

$$\lambda_1 = B_1'(0) - D_1'(0) \quad \text{and}$$

$$\sigma(M_{22}) = \{\lambda_i \,|\, \det(M_{22} - \lambda I) = 0,\ i = 2, 3\}$$

where M_{22} is defined as in (3.13), with $(\mathring{w}, \mathring{z})$ replaced by $(\overline{w}, \overline{z})$. Note that $\mathrm{Re}\,\lambda_2 < 0$ and $\mathrm{Re}\,\lambda_3 < 0$ if $\mathrm{Trace}\, M_{22} < 0$ and $\det M_{22} > 0$.

Theorem 3.3. *The rest point* $\widetilde{E}_1[0,\overline{w},\overline{z}] \in \overline{\mathbb{R}}^+_{x_1wz}$ *is*

(i) *A hyperbolic saddle if*

$$\lambda_1 = B_1'(0) - D_1'(0) > 0$$

and Trace $M_{22} < 0$ *with* det $M_{22} > 0$. *In particular* $\widetilde{E}_1[0,\overline{w},\overline{z}]$ *is repelling in the* x_1*-direction,*

(ii) a *hyperbolic source if*

$$\lambda_1 = B_1'(0) - D_1'(0) > 0$$

and Re $\lambda_i > 0$ *for* $i = 2, 3,$

(iii) *asymptotically stable (sink) if*

$$\lambda_1 = B_1'(0) - D_1'(0) < 0$$

and Trace $M_{22} < 0$ *with* det $M_{22} > 0$.

Proof. Similar to those of the previous subsection.

□

Definition 3.0. A set $\mathcal{A} \subset S$ is a *strong attractor* with respect to S if

$$\limsup_{t\to\infty} \rho(u(t), \mathcal{A}) = 0, \tag{3.19}$$

where $u(t)$ is an orbit such that $u(t_0) \subset S$ and ρ is the Euclidean distance function.

Lemma 3.1. *The invariance box*

$$\mathcal{A}_1 = \left\{(x_1, w, z) \in \mathbb{R}^+_{x_1 wz} | 0 \leq x_1 \leq K_1,\, 0 \leq w \leq -\frac{Q_1}{\delta_1},\, 0 \leq z \leq \frac{Q_2}{\delta_2}\right\} \quad (3.20)$$

where

$$\delta_1 = \max_{w,z} \{\max_{w,z} \widetilde{f}(w,z) - \alpha_1 \min_{w} \widetilde{e}_1(w)\} < 0$$

$$\delta_2 = \alpha_2 \min_{z} \widetilde{e}_2(z) > 0$$

is a strong attractor set with respect to $\mathbb{R}^+_{w_1 wz}$.

Proof. The proof is done using standard comparison theorems as in the previous subsections.

Remark 3.2. Since $\mathcal{A}_1$ is a strong attractor, it implies that all solutions of (3.16) with initial conditions in $\overline{\mathbb{R}}^+_{x_1 wz}$ are dissipative, uniformly bounded, and eventually enter the region $\mathcal{A}_1$.

Theorem 3.4 Existence of $E_1[\overline{x}_1, 0, w, \overline{z}]$. *Suppose*

(i) *Lemma* 3.1 *holds.*

(ii) $\widetilde{E}_1(0, \overline{w}, \overline{z})$ *is a unique hyperbolic rest point in* $\overline{\mathbb{R}}^+_{x_1 wz}$ *and repelling locally*

in the x_1 direction, cf. (Theorem 3.3(i)).

(iii) *No periodic nor homo/heteroclinic orbits exist in the planes of $\overline{\mathbb{R}}^+_{x_1wz}$,* $(\int_0^T (B_1'(0) - D_1'(0))dt > 0)$.

Then

$$\liminf_{t\to\infty} x_1(t) > 0,$$

$$\liminf_{t\to\infty} w(t) > 0,$$

$$\liminf_{t\to\infty} z(t) > 0.$$

In particular, the subsystem in $\overline{\mathbb{R}}^+_{x_1wz}$ exhibits uniform persistence and consequently, the rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ exists.

Proof. The proof follows from the definition of uniform persistence by Butler et al. [1], Freedman and Rai [5,8].

The Jacobian matrix due to linearization around the rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ and using hypotheses H1-H4, and $P_1 - P_6$ and expression (3.11) is given by

$$J_{E_1[\overline{x}_1,0,\overline{w},\overline{z}]} = \begin{bmatrix} B_1'(\overline{x}_1) - D_1'(\overline{x}_1) & -\overline{x}_1 q_1(\overline{x}_1, 0) & 0 & 0 \\ 0 & B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0, w) & 0 & 0 \\ 0 & -\beta h_{x_2}(0, w) & f_w(w, z) - \alpha_1 e_1'(w) & f_z(w, z) \\ 0 & 0 & -\eta f_w(w, z) & -\alpha_2 e_2'(z) - \eta f_z(w, z) \end{bmatrix}. \tag{3.21}$$

The corresponding eigenvalues of the Jacobian matrix for $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ are given by:

$$\lambda_1 = B_1'(\overline{x}_1) - D_1'(\overline{x}_1)$$

$$\lambda_2 = B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0, \overline{w})$$

and λ_3, λ_4 which belong to the set

$$\sigma(M_{22} = \{\lambda_i | \lambda^2 - (\text{Trace } M_{22})\lambda + \det M_{22} = 0\}$$

where M_{22} is defined by (3.13).

Theorem 3.5. *Let*

(i) $B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0, \overline{w}) > 0$

(ii) $B_1'(\overline{x}_1) - D_1'(\overline{x}_1) < 0$

(iii) $\text{Trace } M_{22} < 0$ *and* $\det M_{22} > 0$.

Then the equilibrium $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *is a hyperbolic saddle point and repelling in the* x_2*-direction locally. In particular, the stable manifold,* $W^+(E_1(\overline{x}_1, 0, \overline{w}, \overline{z}))$ *is the* $x_1 - w - z$ *space and the unstable manifold* $W^-(E_1(\overline{x}_1, 0, \overline{w}, \overline{z}))$ *is the* x_2*-direction, with* $\text{Dim } W^-(E_1) = 1$.

□

Theorem 3.6. *The rest point* $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *is locally asymptotically stable (hyperbolic sink) if* $B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0, w) < 0$, $B_1'(\overline{x}_1) - D'(\overline{x}_1) < 0$ *and* Trace $M_{22} < 0$ *with* det $M_{22} > 0$.

The proofs of Theorems 3.5 and 3.6 follow from an inspection of the Jacobian matrix of linearization in the neighborhood of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ and using the Routh-Hurwitz criteria.

The existence and stability of $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$

We now establish criteria for the existence and stability of the rest point $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$.

When system (3.0) is restricted to $\overline{\mathbb{R}}^+_{x_2wz}$, we obtain the following subsystem:

$$\begin{cases} \dot{x}_2 = B_2(x_2) - D_2(x_2) - h(x_2, w) \\ \dot{w} = Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w) \\ \dot{z} = Q_2 - \alpha_2 e_2(z) - \eta f(w, z) \\ x_2(0) = x_{20} \geq 0, \quad w(0) = w_0 \geq 0, \quad z(0) = z_0 \geq 0. \end{cases} \tag{3.22}$$

The possible equilibria corresponding to the system (3.22) are in $\overline{\mathbb{R}}^+_{x_2wz}$

(i) $\widetilde{E}_2[0, \widehat{w}, \widehat{z}]$ and

(ii) $\widetilde{E}_2[\widehat{x}_2, \widehat{w}, \widehat{z}]$.

Using the arguments from Lemma 3.0 we can conclude that the rest point $\widetilde{E}_2[0, \widehat{w}, \widehat{z}]$

exists if there exist $(\widehat{w}, \widehat{z})$ such that

$$Q_1 - \alpha_1 e_1(\widehat{w}) + \frac{1}{\eta}\left(Q_2 - \alpha_2 e_2(\widehat{z})\right) = 0$$

as $t \to \infty$.

The existence of $\widetilde{E}_2[\widehat{x}_2, \widehat{w}, \widehat{z}]$ and hence $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ will be established similar to the previous subsection using persistence analyses.

The Jacobian matrix $DF(\widetilde{E}_2[0, \widehat{w}, \widehat{z}])$ due to linearization of (3.22) in the neighborhood of $\widetilde{E}_2[0, \widehat{w}, \widehat{z}]$ in $\overline{\mathbb{R}}^+_{x_2 wz}$ satisfies the ordinary differential equation

$$\dot{\eta} = DF(\widetilde{E}_2[0, \widehat{w}, \widehat{z}])\eta \tag{3.23}$$

where

$$DF(\widetilde{E}_2[0, \widehat{w}, \widehat{z}]) = \begin{bmatrix} B_2'(0) - D_2'(0) \\ -h_{x_2}(0, \widehat{w}) & 0 & 0 \\ -\beta h_{x_2}(0, \widehat{w}) & \begin{matrix} -\alpha_1 e_1'(\widehat{w}) \\ +f_w(\widehat{w}, \widehat{z}) \end{matrix} & f_z(\widehat{w}, \widehat{z}) \\ 0 & -\eta f_w(\widehat{w}, \widehat{z}) & \begin{matrix} -\alpha_2 e_2'(\widehat{z}) \\ -\eta f_z(\widehat{w}, \widehat{z}) \end{matrix} \end{bmatrix}. \tag{3.24}$$

The hypotheses H1-H4 and $P_1 - P_6$ are again used in the computation of the entries of the Jacobian matrix together with expression (3.11).

The eigenvalues of $DF(\widetilde{E}_2[0,\widehat{w},\widehat{z}])$ are given by

$$\lambda_1 = B_2'(0) - D_2'(0) - h_{x_2}(0,w)$$

and $\lambda_2, \lambda_3 \in \sigma(M_{22})$.

Theorem 3.7. *The rest point* $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ *of* (3.22) *is such that*

(i) $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ *is a hyperbolic saddle point (repelling, in the* x_2*-direction) if* $B_2'(0) - D_2'(0) - h_{x_2}(0,\widehat{w}) > 0$ *and* Trace $M_{22} < 0$ *with* det $M_{22} > 0$.

(ii) $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ *is a hyperbolic source if* $B_2'(0) - D_2'(0) - h_{x_2}(0,w) > 0$ *and* $\mathrm{Re}\,\lambda_i > 0,\ i = 2,3$.

(iii) $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ *is a hyperbolic sink and hence locally asymptotically stable if* $B_2'(0) - D_2'(0) - h_{x_2}(0,\widehat{w}) < 0$ *and* Trace $M_{22} < 0$ *with* det $M_{22} > 0$.

Proof. These result follow immediately from inspection of the Jacobian matrix due to linearization of (3.22) around $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ and applying the qualitative theory of ordinary differential equations.

□

Lemma 3.2. *The (non-negatively) invariant set*

$$\mathcal{A}_2 = \left\{(x_2,w,z) \in \overline{\mathbb{R}}^+_{x_2wz} | 0 \le x_2 \le K_2,\ 0 \le w \le -\frac{Q_1}{\delta_1},\ 0 \le z \le \frac{Q_2}{\delta_2}\right\} \quad (3.25)$$

where δ_1 *and* δ_2 *are defined as in* (3.2) *and* (3.4) *respectively, is a strong attractor with respect to solutions initiating from* $\operatorname{int}\mathbb{R}^+_{x_2wz}$ *with non-negative initial conditions.*

Proof. Similar to the previous subsection proof for the invariant set $\mathcal{A}_1$.

□

Remark 3.3. Since the compact set $\mathcal{A}_2$ is a strong attractor, it therefore means that, all solutions of (3.22) with initial conditions in $\operatorname{int}\mathbb{R}^+_{x_2wz}$ are dissipative, uniformly bounded, and eventually enter the region $\mathcal{A}_2$.

Theorem 3.8 Existence of $E_2[0,\widehat{x}_2,\widehat{w},\widehat{z}]$. *Suppose*

(i) *Lemma* 3.2 *holds.*

(ii) $\widetilde{E}_2[0,\widehat{w},\widehat{z}]$ *is a unique hyperbolic saddle repelling in the* x_2 *direction of* $\overline{\mathbb{R}}^+_{x_2wz}$ *(cf. Theorem* 3.7(i)).

(iii) *There are no periodic nor homo/hetero-clinic trajectories in the planes of* $\overline{\mathbb{R}}^+_{x_2wz}$

$$\Big(\int_0^T [B_2'(0) - D_2'(0) - h_{x_2}(0,w)]dt > 0\Big).$$

Then the subsystem (3.22) *exhibits uniform persistence and the interior equilibrium* $\widetilde{E}[\widehat{x}_2,\widehat{w},\widehat{z}]$ *exists in* $\overline{\mathbb{R}}^+_{x_2wz}$ *and consequently* $E_2[0,\widehat{x}_2,\widehat{w},\widehat{z}]$ *exists.*

Proof. The proof is similar to that for the existence of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ in Section 3.3.2.

□

We now perform the linearized stability analyses for the rest point $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$. The Jacobian matrix due to linearization of system 3.22 in the neighborhood of $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ is given by the expression:

$J_{E_2[0,\widehat{x}_2,\widehat{w},\widehat{z}]} =$

$$\begin{bmatrix} B_1'(0) - D_1'(0) \\ -\widehat{x}_2 q_1(0, \widehat{x}_2) & 0 & 0 & 0 \\ -\widehat{x}_2 q_2(0, \widehat{x}_2) & \begin{matrix} B_2'(\widehat{x}_2) - D_2'(\widehat{x}_2) \\ -h_{x_2}(\widehat{x}_2, \widehat{w}) \end{matrix} & -h_w(\widehat{x}_2, \widehat{w}) & 0 \\ 0 & -\beta h_{x_2}(\widehat{x}_2, \widehat{w}) & \begin{matrix} f_w(\widehat{w}, \widehat{z}) - \alpha_1 e_1'(\widehat{w}) \\ -\beta h_w(\widehat{x}_2, \widehat{w}) \end{matrix} & f_z(\widehat{w}, \widehat{z}) \\ 0 & 0 & -\eta f_w(\widehat{w}, \widehat{z}) & \begin{matrix} -\alpha_2 e_2'(\widehat{z}) \\ -\eta f_z(\widehat{w}, \widehat{z}) \end{matrix} \end{bmatrix}. \tag{3.26}$$

The eigenvalues of $J_{E_2[0,\widehat{x}_2,\widehat{w},\widehat{z}]}$ are given by

$$\lambda_1 = B_1'(0) - D_1'(0) - \widehat{x}_2 q_1(0, \widehat{x}_2)$$

and $\lambda_2, \lambda_3, \lambda_4 \in \sigma(M_{33})$.

In particular M_{33} is the matrix defined by

$$M_{33} = \begin{pmatrix} B_2'(\hat{x}_2) - D_2'(\hat{x}_2) & -h_w(\hat{x}_2, \hat{w}) & 0 \\ -h_{x_2}(\hat{x}_2, \hat{w}) & & \\ -\beta h_{x_2}(\hat{x}_2, \hat{w}) & f_w(\hat{w}, \hat{z}) - \alpha_1 e_1'(\hat{w}) & f_z(\hat{w}, \hat{z}) \\ & -\beta h_w(\hat{x}_2, \hat{w}) & \\ 0 & -\eta f_w(\hat{w}, \hat{z}) & -\alpha_2 e_2'(\hat{z}) \\ & & -\eta f_z(\hat{w}, \hat{z}) \end{pmatrix}$$

$$=: \begin{pmatrix} \hat{m}_{11} & \hat{m}_{12} & \hat{m}_{13} \\ \hat{m}_{21} & \hat{m}_{22} & \hat{m}_{23} \\ \hat{m}_{31} & \hat{m}_{32} & \hat{m}_{33} \end{pmatrix}. \tag{3.27}$$

Now

$$\sigma(M_{33}) = p(\lambda, M_{33}) = \det [M_{33} - \lambda I_3]$$

$$= \{\lambda_i | \lambda^3 + \hat{a}_1 \lambda^2 + \hat{a}_2 \lambda + \hat{a}_3 = 0,\ i = 2, 3, 4\} \tag{3.28}$$

where

$$\hat{a}_1 = -(\text{Trace } M_{33}) = -(\hat{m}_{11} + \hat{m}_{22} + \hat{m}_{33})$$

$$\hat{a}_2 = \det \begin{vmatrix} \hat{m}_{22} & \hat{m}_{23} \\ \hat{m}_{32} & \hat{m}_{33} \end{vmatrix} + \det \begin{vmatrix} \hat{m}_{11} & \hat{m}_{13} \\ \hat{m}_{31} & \hat{m}_{33} \end{vmatrix} + \det \begin{vmatrix} \hat{m}_{11} & \hat{m}_{12} \\ \hat{m}_{21} & \hat{m}_{22} \end{vmatrix}$$

$$\hat{a}_3 = -\det M_{33}. \tag{3.29}$$

Lemma 3.3. *The eigenvalues of* M_{33} *have negative real parts if*

$$\hat{a}_1 > 0, \quad \hat{a}_3 > 0 \quad \text{and} \quad \hat{a}_1 \hat{a}_2 > \hat{a}_3.$$

Proof. The proof uses the Routh-Hurwitz criterion.

Theorem 3.9. *Let*

(i) $B_1'(0) - D_1'(0) - \widehat{x}_2 q_1(0, \widehat{x}_2) > 0$

(ii) $\widehat{a}_1 > 0, \quad \widehat{a}_3 > 0$ *and* $\widehat{a}_1\widehat{a}_2 > \widehat{a}_3$.

Then $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ *is a hyperbolic saddle point and repelling in the* x_1*-direction. In particular, the stable manifold* $W^+(E_2)$ *is the* $x_2 - w - z$ *space and the unstable manifold* $W^-(E_2)$ *is the* x_1*-direction, such that* Dim $W^+(E_2) = 3$ *and* Dim $W^-(E_2) = 1$.

Theorem 3.10. $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ *is locally asymptotically stable (hyperbolic sink) if*

(i) $B_1'(0) - D_1'(0) - \widehat{x}_2 q_1(0, \widehat{x}_2) < 0$ *and*

(ii) $\widehat{a}_1 > 0, \quad \widehat{a}_3 > 0, \quad \widehat{a}_1\widehat{a}_2 > \widehat{a}_3$ *hold concurrently.*

□

The proofs of Theorems 3.9 and 3.10 follow directly from linearized stability analysis and application of the Routh-Hurwitz criteria.

Remark 3.4. The equilibrium $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ corresponds to the scenario in which the *normal* cells in the cancer-affected tissue or organ are all destroyed. This will eventually lead to the demise of the cancer patient unless a transplant of a new organ is implemented. Thus $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ is highly clinically unstable.

Existence of $E_3[x_1^*, x_2^*, w^*, z^*]$

In this section, we shall establish sufficient conditions for the existence of a positive interior equilibrium $E_3[x_1^*, x_2^*, w^*, z^*]$. This will be done by showing that the system (3.0) is uniformly persistent, cf. Freedman and Rai [5,8], Freedman and Waltman [9].

To show uniform persistence in $\overline{\mathbb{R}}^+_{x_1x_2wz}$ we must assume or verify the following hypotheses for system (3.0).

H_0 : All dynamics are trivial on $\partial\overline{\mathbb{R}}^+_{x_1x_2wz}$

H_1 : All invariant sets (equilibria/rest points) are hyperbolic and isolated.

H_2 : No invariant sets on $\partial\overline{\mathbb{R}}^+_{x_1x_2wz}$ are asymptotically stable.

H_3 : If an equilibrium exists in the *interior* of any 3-dimensional subspace of $\overline{\mathbb{R}}^+_{x_1x_2wz}$, it must be globally asymptotically stable with respect to orbits initiating in that interior.

H_4 : If M is an invariant set on $\partial\overline{\mathbb{R}}^+_{x_1x_2wz}$, and $W^+(M)$ is its strong stable manifold, then

$$W^*(M) \cap \text{int } \mathbb{R}_{x_1x_2wz} = \emptyset. \tag{3.30}$$

H_5 : The given system of differential equations is dissipative and eventually uniformly bounded for $t \in \mathbb{R}_+$ with respect to a strong (compact) attractor set.

H_6 : All invariant sets are *acyclic.*

Remark 3.5. $H_1 - H_5$ gives persistence and H_6 is required for uniform persistence.

3.6. Global Asymptotic Stability of $\overline{E}_1[\overline{x}_1, \overline{w}, \overline{z}]$

In this subsection criteria for the global asymptotic stability of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ with respect to solutions initiating in int $\mathbb{R}^+_{x_1wz}$ will be established.

In $\mathbb{R}^+_{x_1wz}$ we choose the Liapunov function,

$$V(x_1, w, z) = x_1 - \overline{x}_1 - \overline{x}_1 \ell n \frac{x_1}{\overline{x}_1} + \frac{1}{2} k_1(w - \overline{w})^2 + \frac{1}{2} k_2(z - \overline{z})^2 \qquad (3.31)$$

where $k_i \in \mathbb{R}_+$ for $i = 1, 2$.

The derivative of (3.31) along the solution curves of (3.16) in $\overline{\mathbb{R}}^+_{x_1wz}$ is given by the expression:

$$\begin{aligned} \dot{V} = &(x_1 - \overline{x}_1) g_1(x_1) \\ &+ k_1(w - \overline{w})[Q_1 - \alpha_1 e_1(w) + f(w, z)] \\ &+ k_2(z - \overline{z})[Q_2 - \alpha_2 e_2(z) - \eta f(w, z)] \end{aligned} \qquad (3.32)$$

where we set

$$B_i(x_i) - D_i(x_i) \equiv x_i g_i(x_i), \quad i = 1, 2. \qquad (3.33)$$

Thus

$$\begin{aligned}\dot{V} &= (x_1 - \overline{x}_1)g_1(x_1) \\ &+ k_1(w - \overline{w})\alpha_1[e_1(\overline{w}) - e_1(w)] + k_1(w - \overline{w})[f(w,z) - f(\overline{w},\overline{z})] \\ &+ k_2(z - \overline{z})\alpha_2[e_2(\overline{z}) - e_2(z)] + k_2(z - \overline{z})\eta[f(\overline{w},\overline{z}) - f(w,\overline{z})].\end{aligned} \tag{3.34}$$

Let $X = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix}$ such that $\begin{matrix} v_1 = x_1 - \overline{x}_1 \\ v_2 = w - \overline{w} \\ v_3 = z - \overline{z} \end{matrix}$ and set

$$\left.\begin{aligned} a_{11} &= \tfrac{g_1(x_1)}{x_1 - \overline{x}_1}, \quad a_{12} = 0, \quad a_{13} = 0 \\ a_{22} &= -k_1\alpha_1 \tfrac{[e_1(w) - e_1(\overline{w})]}{(w - \overline{w})} \\ a_{23} &= k_1 \tfrac{[f(w,z) - f(\overline{w},\overline{z})]}{(z - \overline{z})} - \eta k_2 \tfrac{[f(w,\overline{z}) - f(\overline{w},\overline{z})]}{(w - \overline{w})} \\ a_{33} &= -k_2\alpha_2 \tfrac{[e_2(z) - e_2(\overline{z})]}{(z - \overline{z})}. \end{aligned}\right\} \tag{3.35}$$

Thus

$$\begin{aligned}\dot{V} &= a_{11}v_1^2 + a_{22}v_2^2 + a_{23}v_2v_3 + a_{33}v_3^2 \\ &= a_{11}v_1^2 + \frac{1}{2}a_{12}v_1v_2 + \frac{1}{2}a_{13}v_1v_3 \\ &\quad + \frac{1}{2}a_{12}v_1v_2 + a_{22}v_2v_2 + \frac{1}{2}a_{23}v_2v_3 \\ &\quad + \frac{1}{2}a_{13}v_1v_3 + \frac{1}{2}a_{23}v_2v_3 + a_{33}v_3^2\end{aligned} \tag{3.36}$$

where $a_{ij} = a_{ji}$ with $a_{12} = a_{13} = 0$.

But

$$\dot{V} = X^T AX = X^T A \cdot X = \langle AX, X \rangle \tag{3.37}$$

where

$$A = \begin{pmatrix} a_{11} & \frac{1}{2}a_{12} & \frac{1}{2}a_{13} \\ \frac{1}{2}a_{12} & a_{22} & \frac{1}{2}a_{23} \\ \frac{1}{2}a_{13} & \frac{1}{2}a_{23} & a_{33} \end{pmatrix} . \tag{3.38}$$

In particular, A is symmetric and real such that $A = \frac{1}{2}(A + A^t)$ where t denotes transpose.

Lemma 3.4 Negative Definiteness of $\dot{V}$.

(i) *$\dot{V}$ is negative if $X^T AX$ is negative definite.*

(ii) *$X^T AX$ is negative if A is negative definite.*

(iii) *A is negative definite if the (eigenvalues) zeros of the polynomial*

$$p(\lambda, A) = \det(A - \lambda I_n) = 0$$

have negative real parts.

□

A complete discussion and proofs of the lemma can be found in references [4,18].

Lemma 3.5 [Frobenius 1876]). *Let*

$$X = \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_n \end{pmatrix}, \quad X^T = (x_1, x_2, x_3, \ldots, x_n) \in \mathbb{R}^n.$$

Let A *be a symmetric* $n \times n$ *matrix over* $\mathbb{R}$. *Then the real quadratic form* $X^T AX$ *is negative definite if* A *is negative definite. In particular, a necessary and sufficient condition for the real, symmetric matrix* A *to be negative definite is that the principal minors of* A, *starting with that of the first order, be alternatively negative and positive.*

□

The discussion of Lemma 3.5 is found in Howard Eves book, cf. [4]. We now state additional hypotheses.

P_9 : Let $\dot{V} = X^T AX$, $A = \{a_{ij}\}_{n \times n}$ where A is a real symmetric $n \times n$ matrix. Then the a_{ij}'s are such that

(i) $a_{ij} \in C'(\mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+, \mathbb{R})$

(ii) $\lim_{x \to \overline{x}} a_{ij}$ exist as a finite number, where $\overline{x}$ is rest point

(iii) the a_{ij} are bounded.

Let the matrix A be given as in (3.38). Then

$$p(\lambda, A) = \det(A - \lambda I)$$

$$= \lambda^3 + \overline{m}_1\lambda^2 + \overline{m}_2\lambda + \overline{m}_3 = 0 \tag{3.39}$$

where

$$\overline{m}_1 = -\operatorname{trace} A = -(a_{11} + a_{22} + a_{23})$$

$$\overline{m}_2 = \det \begin{vmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{12} & a_{22} \end{vmatrix} + \det \begin{vmatrix} a_{11} & \frac{1}{2}a_{13} \\ \frac{1}{2}a_{13} & a_{33} \end{vmatrix} + \det \begin{vmatrix} a_{22} & \frac{1}{2}a_{23} \\ \frac{1}{2}a_{23} & a_{33} \end{vmatrix}$$

$$\overline{m}_3 = -\det A.$$

These reduce with $a_{12} = a_{13} = 0$ to:

$$\left.\begin{aligned} \overline{m}_1 &= -(a_{11} + a_{22} + a_{33}) \\ \overline{m}_2 &= a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{33} - \tfrac{1}{4}a_{23}^2 \\ \overline{m}_3 &= a_{11}(a_{22}a_{33} - \tfrac{1}{4}a_{23}^2). \end{aligned}\right\} \tag{3.40}$$

Hence by the Routh-Hurwitz criterion and Lemma 3.4(iii), the matrix A is negative definite if

$$\overline{m}_1 > 0, \quad \overline{m}_3 > 0 \quad \text{and} \quad \overline{m}_1\overline{m}_2 > \overline{m}_3. \tag{3.41}$$

A refinement of the criteria (3.41) leads to the following theorem:

Theorem 3.11. *The rest point* $\widetilde{E}_1[\overline{x}_1, \overline{w}, \overline{z}] \in \overline{\mathbb{R}}^+_{x_1wz}$ *is globally asymptotically stable with respect to solutions trajectories initiating from* $\operatorname{int} \overline{\mathbb{R}}^+_{x_1wz}$ *if*

(i) $a_{11} < 0, \quad a_{22} < 0, \quad a_{33} < 0$ *and*

(ii) $a_{22}a_{33} - \frac{1}{4}a_{23}^2 > 0.$

In an alternative approach, using Frobenius Theorem, we see that the leading principal minors of A are

$$a_{11}, \quad \det \begin{vmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{12} & a_{22} \end{vmatrix}, \text{ and } \quad \det A.$$

Thus A is negative definite if

$$a_{11} < 0, \quad \det \begin{bmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{12} & a_{22} \end{bmatrix} > 0 \tag{3.42}$$

and let $A < 0$, by Lemma 3.5.

Since $a_{12} = a_{13} = 0$, we arrive at refined criteria for the negative definiteness of A as:

$$\left.\begin{array}{ll} \text{(i)} & a_{11} < 0, \quad a_{22} < 0, \quad a_{33} < 0 \quad \text{and} \\ \text{(ii)} & a_{22}a_{33} - \frac{1}{4}a_{23}^2 > 0. \end{array}\right\} \tag{3.43}$$

This agrees with Theorem 3.11.

Global asymptotic stability of $\widetilde{E}_2[\widehat{x}_2, \widehat{w}, \widehat{z}]$

In this subsection criteria for global asymptotic stability of the 3-dimensional equilibrium $\widetilde{E}_2[\widehat{x}_2, \widehat{w}, \widehat{z}]$ or equivalently $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ with respect to solutions initiating from $\text{int}\, \mathbb{R}^+_{x_2wz}$ will be established.

We consider the subsystem (3.22) and choose the Liapunov function:

$$V = x_2 - \hat{x}_2 - \hat{x}_2 \ell n \frac{x_2}{\hat{x}_2} + \frac{1}{2} k_2 (w - \hat{w})^2 + \frac{1}{2} k_3 (z - \hat{z})^2. \tag{3.44}$$

Let

$$\begin{cases} h(x_2, w) = x_2 h_1(x_2, w) & \text{and} \\ h_1(x_2, w) = w h_2(x_2, w). \end{cases} \tag{3.45}$$

Then using (3.33) and (3.43) we have:

$$\begin{aligned} \dot{V} &= (x_2 - \hat{x}_2)[g_2(x_2) - h_1(x_2, w)] \\ &\quad + k_2(w - \hat{w})[Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w)] \\ &\quad + k_3(z - \hat{z})[Q_2 - \alpha_2 e_2(z) - \eta f(w, z)]. \end{aligned} \tag{3.46}$$

Simplifying (3.44) leads to

$$\begin{aligned} \dot{V} &= (x_2 - \hat{x}_2) g_2(x_2) - (x_2 - \hat{x}_2)[w h_2(x_2, w) - \hat{w} h_2(x_2, \hat{w})] \\ &\quad - (x_2 - \hat{w}_2) \hat{w} h_2(x_2, \hat{w}) \\ &\quad + k_2(w - \hat{w})[\alpha_1(e_1(\hat{w}) - e_1(w))] + k_2(w - \hat{w})[f(w, z) - f(\hat{w}, \hat{z})] \\ &\quad + \beta k_2(w - \hat{w})[h(\hat{x}_2, \hat{w}) - h(x_2, w)] \\ &\quad + k_3(z - \hat{z})[\alpha_2(e_2(\hat{z}) - e_2(z))] + k_3 \eta (z - \hat{z})[f(\hat{w}, \hat{z}) - f(w, \hat{z})]. \end{aligned} \tag{3.47}$$

We now set $\dot{V} = X^T B X$ with $X = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix} = \begin{pmatrix} x_2 - \hat{x}_2 \\ w - \hat{w} \\ z - \hat{z} \end{pmatrix}$ where

$$B = \begin{pmatrix} b_{11} & \frac{1}{2} b_{12} & \frac{1}{2} b_{13} \\ \frac{1}{2} b_{12} & b_{22} & \frac{1}{2} b_{23} \\ \frac{1}{2} b_{13} & \frac{1}{2} b_{23} & b_{33} \end{pmatrix} \quad \text{with} \quad b_{13} = b_{31} = 0. \tag{3.48}$$

Note that $b_{ij} = b_{ji}$. Thus B is a real and symmetric 3×3 matrix, such that

$$B = \frac{1}{2}(B + B^t).$$

In particular the b_{ij}'s are defined as

$$\begin{aligned}
b_{11} &= g_2(x_2) - \hat{w} h_2(x_2, \hat{w}) \\
b_{12} = b_{21} &= \frac{w h_2(x_2, w) - \hat{w} h_2(x_2, \hat{w})}{(w - \hat{w})} + \beta k_2 \frac{h(\hat{x}_2, \hat{w}) - h(x_2, w)]}{(x_2 - \hat{x}_2)} \\
b_{13} = b_{31} &= 0 \\
b_{22} &= k_2 \alpha_1 \frac{[e_1(\hat{w}) - e_1(w)]}{(w - \hat{w})} \\
b_{33} &= k_3 \alpha_2 \frac{[e_2(\hat{z}) - e_2(z)]}{(z - \hat{z})} .
\end{aligned} \tag{3.49}$$

The leading principal minors of B are b_{11}, $\det \begin{vmatrix} b_{11} & \frac{1}{2} b_{12} \\ \frac{1}{2} b_{12} & b_{22} \end{vmatrix}$, and $\det B$. By Frobenius' Theorem, B will be negative definite if

$$\left.\begin{aligned} b_{11} < 0, \quad \det \begin{vmatrix} b_{11} & \frac{1}{2} b_{12} \\ \frac{1}{2} b_{12} & b_{22} \end{vmatrix} > 0 \\ \text{and} \quad \det B < 0. \end{aligned}\right\} \tag{3.50}$$

But $b_{13} = b_{31} = 0$ and hence (3.50) simplifies the criteria:

$$\begin{aligned} &\text{(i)} \quad b_{11} < 0, \quad b_{22} < 0, \quad b_{33} < 0, \quad b_{12} < 0, \\ &\text{(ii)} \quad b_{11}b_{22} - \tfrac{1}{4}\, b_{12}^2 > 0, \\ &\text{(iii)} \quad b_{22}b_{33} - \tfrac{1}{4}\, b_{23}^2 > 0. \end{aligned} \tag{3.51}$$

This leads to the following theorem:

Theorem 3.12. *The rest point* $\widetilde{E}_2[\widehat{x}_2, \widehat{w}, \widehat{z}] \in \overline{\mathbb{R}}^+_{x_2wz}$ *is globally asymptotically stable with respect to solution trajectories initiating from* $\operatorname{int} \overline{\mathbb{R}}^+_{x_2wz}$ *if*

(i) $b_{11} < 0, \quad b_{22} < 0, \quad b_{33} < 0, \quad b_{12} < 0$ *and*

(ii) $b_{11}b_{22} - \frac{1}{4}\, b_{12}^2 > 0$

(iii) $b_{22}b_{33} - \frac{1}{4}\, b_{23}^2 > 0.$

□

Global asymptotic stability of $E_0[0, 0, \mathring{w}, \mathring{z}]$ **in** $\overline{\mathbb{R}}^+_{wz}$

Consider system (3.0) restricted to $\overline{\mathbb{R}}^+_{wz}$ as depicted by equations (3.16).

We have shown that the 2-dimensional equilibrium $\widetilde{E}_0[\mathring{w}, \mathring{z}]$ and consequently $E_0[0, 0, \mathring{w}, \mathring{z}]$ exists if Lemma 3.0 holds. In this subsection we shall establish criteria for the global asymptotic stability of $E_0[0, 0, \mathring{w}, \mathring{z}]$ with respect to solutions emanating from the interior of $\overline{\mathbb{R}}^+_{wz}$.

Let G be a neighborhood of any point in $\mathbb{R}^+_{wz}$. We choose the Liapunov

function V such that:

$$V = \frac{1}{2}\, c_1(w - \mathring{w})^2 + \frac{1}{2}\, c_2(z - \mathring{z})^2. \tag{3.52}$$

Note that

(i) V is positive definite with respect to $E_0[0, 0, \mathring{w}, \mathring{z}]$ in $\overline{\mathbb{R}}^+_{wz}$.

(ii) $V \to \infty$ as $w^2 + z^2 \to \infty$

(iii) V is a Liapunov function for (3.16) in G

(iv) $V \in C'(\mathbb{R}^2_+, \mathbb{R})$ and is bounded below.

Now

$$\dot{V} = c_1(w - \mathring{w})\dot{w} + c_2[z - \mathring{z}]\dot{z} \tag{3.53}$$

along the solutions trajectories of (3.1). From (3.53) we obtain the expression

$$\begin{aligned} \dot{V} &= c_1(w - \mathring{w})[Q_1 - \alpha_1 e_1(w) + f(w, z)] \\ &\quad + c_2(z - \mathring{z})[Q_2 - \alpha_2 e_2(z) - \eta f(w, z)] \end{aligned} \tag{3.54}$$

or

$$\begin{aligned} \dot{V} &= c_1(w - \mathring{w})[\alpha_1 e_1(\mathring{w}) - f(\mathring{w}, \mathring{z}) - \alpha_1 e_1(w) + f(w, z)] \\ &\quad + c_2(z - \mathring{z})[\alpha_2 e_2(\mathring{z}) + \eta f(\mathring{w}, \mathring{z}) - \alpha_2 e_2(z) - \eta f(w, z)] \\ &= \alpha_1 c_1(w - \mathring{w})[e_1(\dot{w}) - e_1(w)] + c_1(w - \mathring{w})[f(w, z) - f(\mathring{w}, \mathring{z})] \end{aligned}$$

$$+\alpha_2 c_2(z-\overset{\circ}{z})[e_2(\dot{z})-e_2(z)]+\eta c_2(z-\overset{\circ}{z})[f(\overset{\circ}{w},\overset{\circ}{z})-f(w,z)]. \tag{3.55}$$

In particular,

$$\dot{V}=X^TCX \quad \text{where} \quad X=\begin{pmatrix} v_1 \\ v_2 \end{pmatrix}=\begin{pmatrix} w-\overset{\circ}{w} \\ z-\overset{\circ}{z} \end{pmatrix}$$

where

$$C=\begin{pmatrix} c_{11} & \frac{1}{2}c_{12} \\ \frac{1}{2}c_{12} & c_{22} \end{pmatrix} \tag{3.56}$$

and

$$\left.\begin{aligned} c_{11} &= -\alpha_1 c_1 \tfrac{[e_1(w)-e_1(\overset{\circ}{w})]}{(w-\overset{\circ}{w})} \\ c_{12}=c_{21} &= c_1 \tfrac{[f(w,z)-f(\overset{\circ}{w},\overset{\circ}{z})]}{(z-\overset{\circ}{z})} - \eta c_2 \tfrac{[f(w,z)-f(\overset{\circ}{w},\overset{\circ}{z})]}{(w-\overset{\circ}{w})} \\ c_{22} &= -\alpha_2 c_2 \tfrac{[e_2(z)-e_2(\overset{\circ}{z})]}{(z-\overset{\circ}{z})}. \end{aligned}\right\} \tag{3.57}$$

Define

$$\mathcal{A}_0=\left\{(w,z)\in \mathbb{R}^+_{wz} \,|\, 0\le w\le -\frac{Q_1}{\delta_1},\quad 0\le z\le \frac{Q_2}{\delta_2}, \delta_1<0,\ \delta_2>0\right\} \tag{3.58}$$

where δ_1 and d_2 are as defined by expressions (3.2) and (3.4).

We now define the sets

$$S_1=\{(w,z)\in \mathcal{A}_0\cap \operatorname{int}\mathbb{R}^+_{wz} \,|\, V(w,z)=0\} \tag{3.59}$$

$$S_2=\{(w,z)\in \operatorname{int}\mathbb{R}^+_{wz} \,|\, w=\overset{\circ}{w},\ z=\overset{\circ}{z}\}. \tag{3.60}$$

By inspection, we see immediately that

$$S_1 \equiv S_2.$$

Now define the set $\mathbf{E}$ as follows:

$$\mathbf{E} = \{(w,z) \in \mathbb{R}^+_{wz} | \dot{V} = 0\} \cap \overline{G}. \tag{3.61}$$

Then the *largest invariant set* in $\mathbf{E}$ is $E_0(0,0,\mathring{w},\mathring{z})$ restricted to $\mathbb{R}^+_{wz}$.

Hence by LaSalle's Invariant Principle, cf. [17.18,21], we conclude that $\widetilde{E}_0[\mathring{w},\mathring{z}]$ or consequently $E_0[0,0,\mathring{w},\mathring{z}]$ is globally asymptotically stable with respect to solutions initiating from $\operatorname{int}\mathbb{R}^+_{wz}$ if the matrix C is negative definite.

Theorem 3.13. *The equilibrium* $E_0(0,0,\mathring{w},\mathring{z}) \in \overline{\mathbb{R}}^+_{wz}$ *is globally asymptotically stable with respect to solution trajectories emanating from* $\operatorname{int}\mathbb{R}^+_{wz}$ *if*

(i) $c_{11} < 0, \quad c_{22} < 0$ *and*

(ii) $c_{11}c_{22} - \frac{1}{4}c_{12}^2 > 0.$

Proof. The proof follows from computing the leading principal minors of (3.56) and using the Frobenius Theorem, cf. Lemma 3.5 or alternatively by means of Lemma 3.4.

□

3.7. Persistence, Uniform Persistence and Existence of $E_3[x_1^*, x_2^*, w^*, z^*]$

In this subsection we shall present results on persistence, uniform persistence and finally give sufficient criteria for the existence of a positive interior equilibrium $E_3[x_1^*, x_2^*, w^*, z^*]$.

Theorem 3.14. *Assume* (3.0) *is such that*

(i) $E_0(0, 0, \mathring{w}, \mathring{z})$ *is a hyperbolic saddle and repelling in the* x_1 *and* x_1 *directions locally (cf. Theorem* 3.3*)*

(ii) $E_1(\overline{x}_1, 0, \overline{w}, \overline{z})$ *is a hyperbolic saddle and repelling in the* x_2 *direction locally (cf. Theorem* 3.7*)*

(iii) $E_2(0, \widehat{x}_2, \widehat{w}, \widehat{z})$ *is a hyperbolic saddle and repelling in the* x_1*-direction locally (cf. Theorem* 3.9*)*

(iv) *system* (3.0) *is dissipative and solutions initiating in* $\operatorname{int} \overline{\mathbb{R}}^+_{x_1x_2wz}$ *are eventually uniformly bounded (cf. Theorem* 3.0*)*

(v) *the equilibria* $E_0(0, 0, \mathring{w}, \mathring{z})$, $E_1(\overline{x}_1, 0, \overline{w}, \overline{z})$ *and* $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ *are globally asymptotically stable with respect to* $\overline{\mathbb{R}}^+_{wz}$, $\overline{\mathbb{R}}^+_{x_1wz}$ *and* $\overline{\mathbb{R}}^+_{x_2wz}$ *respectively, cf. [Theorems* 3.13, 3.11, 3.12*].*

Then system (3.0) *exhibits (robust) persistence.*

Proof. The proof will be done using the Butler-McGehee Lemma (see Chapter 1).

Let

$$\mathbb{B} = \Big\{(x_1, x_2, w, z) \in \mathbb{R}^+_{x_1 x_2 w z} | 0 \le x_1 \le K_1,\ 0 \le x_2 \le K_2,$$
$$0 \le w \le -\frac{Q_1}{\delta_1},\ 0 \le z \le \frac{Q_2}{\delta_2}\Big\} \subset \mathbb{R}^4_+$$

where δ_1, and δ_2 are as defined by (3.2).

We have shown in Theorem 3.0 that $\mathbb{B}$ is positively invariant and any solution of (3.0) initiating at a point in $\mathbb{B} \subset \mathbb{R}^4_+$ is eventually bounded.

But $E_0 = E_0(0, 0, \overset{\circ}{w}, \overset{\circ}{z})$, $E_1 = E_1(\overline{x}_1, 0, \overline{w}, \overline{z})$ and $E_2 = E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ are the only compact invariant sets on $\partial\mathbb{R}^4_+$. Let $M = E_3[x_1^*, x_2^*, w^*, z^*]$ be such that $M \in \text{int}\,\mathbb{R}^4_+$.

The proof is completed by showing that *no* point $Q_i \in \partial\mathbb{R}^4_+$ belongs to $\Omega(M)$. The proof is divided into five steps.

Step 1: We show that:

$$E_0 \notin \Omega(M).$$

Suppose $E_0 \in \Omega(M)$. Since E_0 is hyperbolic, $E_0 \neq \Omega(M)$. By the Butler-McGehee Lemma, there exists a point $Q_0^+ \in W^+(E_0)\backslash\{E_0\})$ such that $Q_0^+ \in \Omega(M)$. But $W^+(E_0) \cap (\mathbb{R}^4_+ \backslash \{E_0\}) = \emptyset$. This contradicts the positive invariance property of $\mathbb{B} \subset \mathbb{R}^4_+$. Thus $E_0 \notin \Omega(M)$.

Step 2. We show that:

$$E_1 \notin \Omega(M).$$

If $E_1 \in \Omega(M)$, then there exists a point $Q_1^+ \in W^+(E_1)\backslash\{E_1\}$ such that $Q_1^+ \in \Omega(M)$ by the Butler-McGehee Lemma. But $W^+(E_1) \cap (\text{int } \mathbb{R}^4_+) = \emptyset$ and $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ is globally asymptotically stable with respect to $\mathbb{R}^+_{x_1wz}$. This implies that the closure of the orbit $\overline{O(Q_1^+)}$ through Q_1^+ either contains E_0 or is unbounded. This is a contradiction. Hence $E_1 \notin \Omega(M)$.

Step 3. We show that:

$$E_2 \notin \Omega(M).$$

The proof is similar to Step 2.

Step 4. We show that:

$$\partial\mathbb{R}^4_+ \cap \Omega(M) = \emptyset.$$

Suppose $\partial\mathbb{R}^4_+ \cap \Omega(M) \neq \emptyset$. Let $Q \in \partial\mathbb{R}^4_+$ and $Q \in \Omega(M)$. Then, the closure of the orbit through Q, i.e. $\overline{O(Q)}$ must either contain E_0, E_1, E_2 or is unbounded.

This gives a contradiction.

Step 5. Thus we see that if E_0 is unstable then

$$W^+(E_0) \cap (\mathbb{R}^4_+ | \{E_0\}) = \emptyset.$$

Also, we deduce that if E_1 is unstable, then

$$W^+(E_1) \cap (\text{int } \mathbb{R}^4_+) = \emptyset$$

$$W^-(E_1) \cap (\mathbb{R}^4 \backslash \mathbb{R}^4_+) \neq \emptyset.$$

Similarly if E_2 is unstable, then

$$W^+(E_2) \cap (\text{int } \mathbb{R}^4_+) = \emptyset$$

$$W^-(E_1) \cap (\mathbb{R}^4 \backslash \mathbb{R}^4_+) \neq \emptyset$$

and the persistence result follows since $\Omega(M)$ must be in $\inf \mathbb{R}^4_+$.

□

Remark 3.9. The global asymptotic stability of the equilibria E_0, E_1, and E_2 with respect to $\mathbb{R}^+_{wz}$, $\mathbb{R}^+_{x_1wz}$ and $\mathbb{R}^+_{x_2wz}$ respectively, implies that the boundary flow is *isolated* and *acyclic* with respect to $\mathcal{C}$.

Theorem 3.15. *Let the conditions of Theorem* 3.14 *hold. Then system* (3.0) *exhibits uniform persistence. In particular, a positive interior equilibrium of the form* $E_3[x_1^*, x_2^*, w^*, z^*]$ *exists.*

Proof. The results follow directly from the results obtained [1].

□

3.8. Hopf-Andronov-Poincaré Bifurcation

In this section, the Hopf-Andronov-Poincaré bifurcation, cf. Wiggins [31], will be performed on the system of equations (3.0) with bifurcation parameter

μ. In particular the parameter μ is chosen such that the activation-proliferation function f is a function of μ. The system of equations now takes the form:

$$\left.\begin{aligned} \dot{x}_1 &= B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) \\ \dot{x}_2 &= B_2(x_2) - B_2(x_2) - x_1 x_2 q_2(x_1, x_2) - h(x_2, w) \\ \dot{w} &= Q_1 - \alpha_1 e_1(w) + f(w, z; \mu) - \beta h(x_2, w) \\ \dot{z} &= Q_2 - \alpha_2 e_2(z) - \eta f(w, z; \mu) \\ x_1(0) &= x_{10} \geq 0, \quad x_2(0) = x_{20} \geq 0 \\ w(0) &= w_0 \geq 0, \quad z(0) = z_0 \geq 0. \end{aligned}\right\} \tag{3.62}$$

System (3.62) can be recast into the form

$$\begin{aligned} \dot{x} &= F(x; \mu) \\ x(0) &= x_0 \end{aligned} \tag{3.63}$$

where $x \in \mathbb{R}^4 = \begin{pmatrix} x_1 \\ x_2 \\ w \\ z \end{pmatrix}$.

$\mu \in \mathbb{R}^1$ is the bifurcation parameter. $F(x, \mu)$ is a C^r $(r \geq 5)$ function on an open set in $\mathbb{R}^4 \times \mathbb{R}^1$. Let

$$\begin{aligned} \mathbb{P}_\mu = [&E_0(0, 0, \mathring{w}, \mathring{z}; \mu), E_1(\overline{x}_1, 0, \overline{w}, \overline{z}; \mu), \\ &E_2(0, \widehat{x}_2, \widehat{w}, \widehat{z}; \mu), E_3(x_1^*, x_2^*, w^*, z^*; \mu)] \end{aligned} \tag{3.64}$$

be the set of rest (fixed) points of (3.62) such that

$$F(\mathbb{P}_\mu) = 0 \quad \text{for some} \quad \mu \in \mathbb{R}^1$$

on a sufficiently large open set G containing each member of $\mathbb{P}_\mu$.

The linear vector field obtained by linearizing (3.6 2) about any μ is given by

$$\dot{\xi} = DF(\mathrm{IP}_\mu)\xi, \quad \xi \in \mathbb{R}^4.$$

We are interested in studying how the orbit structure near IP_μ changes as μ is varied.

IP_{10} : [The Technicality Criterion]

Let

$$\frac{d}{d\mu}\left[f_w(w,z;\mu) - \eta f_z(w,z;\mu)\right] > 0 \tag{3.65}$$

for $\mu = \mu_0$ at $(w,z) = (\overline{w},\overline{z})$.

Theorem 3.16. *Suppose Theorems* 3.3 *and* 3.9 *hold. Then Hopf bifurcation cannot occur at* E_0 *and* E_2.

Proof. This follows from the fact that when Theorems 3.3 and 3.9 hold respectively then E_0 and E_2 are hyperbolic saddle points and their stable manifolds lie along an axis.

□

Next we have to compute stability criteria for $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}, \mu]$ and $E_3[x_1^*, x_2^*, w^*, z^*, \mu]$ and then vary μ in order to obtain the desired Hopf bifur-

cation for $\mu = \nu_1$ and $\mu = \nu_2$ around E_1 and E_2 respectively.

Hopf bifurcation analysis for $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}, \mu]$

Let

$$J_\mu(P_1) = DF\big(E_1(\overline{x}_1, 0, \overline{w}, \overline{z}, \mu)$$
$$= \begin{pmatrix} \overline{A}_{11}(\mu) & 0 \\ \overline{A}_{21}(\mu) & \overline{A}_{22}(\mu) \end{pmatrix}, \quad \overline{A}_{21}(\mu) = \begin{pmatrix} 0 & -\beta h_{x_2}(0,w) \\ 0 & 0 \end{pmatrix}$$

where

$$\overline{A}_{11} = \begin{bmatrix} B_1'(\overline{x}_1) - D_1'(\overline{x}_1) & -\overline{x}_1 q_1(\overline{x}_1, 0) \\ 0 & B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0,w) \end{bmatrix}$$

$$\overline{A}_{22} = \begin{bmatrix} f_w(\overline{w}, \overline{z}; \mu) - \alpha_1 e_1'(\overline{w}) & f_z(\overline{w}, \overline{z}; \mu) \\ -\eta f_w(\overline{w}, \overline{z}; \mu) & -\alpha_2 e_2'(z) - \eta f_z(\overline{w}, \overline{z}; \mu) \end{bmatrix}.$$

The eigenvalues of $J_\mu(P_1)$ are

$$\lambda_1 = B_1'(\overline{x}_1) - D_1'(\overline{x}_1)$$
$$\lambda_2 = B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0,w) \tag{3.66}$$

and the solution of

$$p(\lambda, \overline{A}_{22}) = \det |\overline{A}_{22} - \lambda I_2| = 0$$
$$= \lambda^2 - (\text{Trace } \overline{A}_{22})\lambda + \det \overline{A}_{22} = 0. \tag{3.67}$$

Let $\lambda_{3,4} = \{\lambda | p(\lambda, \overline{A}_{22}) = 0\}$. Then

$$\lambda_{3,4} = \frac{1}{2}\left[\text{Trace } \overline{A}_{22} \pm \sqrt{(\text{Trace } \overline{A}_{22})^2 - 4 \det \overline{A}_{22}}\,\right]. \tag{3.68}$$

Theorem 3.17. *The Jacobian matrix* $J_\mu(\mathbb{P}_1)$ *has two negative real roots and two purely imaginary roots if the following criteria hold concurrently*

(i) $\lambda_1 = B_1'(\overline{x}_1) - D_1'(\overline{x}_1) < 0$

(ii) $\lambda_2 = B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) - h_{x_2}(0, w)$

(iii) *there exists a* $\mu = \nu_1$ *with* Trace $\overline{A}_{22} = 0$

(iv) $\det \overline{A}_{22} > 0$ *with* $\lambda_3, \lambda_4 \in$ im $\mathbb{C}$.

Thus $\frac{d}{d\mu}\,[\text{Re } \lambda_i(\nu_1)] > 0$.

Proof. The proof follows directly from inspecting equations (3.66) and (3.68). Re $\lambda_i = \frac{1}{2}$ Trace $\overline{A}_{22}$ for $i = 3, 4$. But

$$\text{Trace } \overline{A}_{22} = f_w(\overline{w}, \overline{z}; \mu) - \alpha_1 e_1'(w) - \alpha_2 e_2'(\overline{z}) - \eta f_z(\overline{w}, \overline{z}; \mu).$$

Thus

$$\begin{aligned}\frac{d}{d\mu}\left[\operatorname{Re}\lambda_i\right] &= \left[\operatorname{Re}\frac{d}{d\mu}\lambda_i\right]_{\mu=\nu_1} \\ &= \frac{d}{d\mu}\left[f_w(\overline{w},\overline{z};\mu) - \alpha_1 e_1'(\overline{w}) - \alpha_2 e_2'(\overline{z}) - \eta f_z(\overline{w},\overline{z};\mu)\right]_{\mu=\nu_1} \\ &= \frac{d}{d\mu}\left[f_w(\overline{w},\overline{z};\mu) - \alpha_1 e_1'(\overline{w}) - \alpha_2 e_2'(\overline{z}) - \eta f_z(\overline{w},\overline{z};\mu)\right]_{\mu=\nu_1} \\ &= f_{w\mu}(\overline{w},\overline{z};\nu_1) - \eta f_{z\mu}(\overline{w},\overline{z};\nu_1) > 0 \qquad (3.69)\end{aligned}$$

by $\mathbb{P}_{10}$.

□

Theorem 3.18. *Suppose*

(i) $\operatorname{Tr}\overline{A}_{22} = 0$ *for some* $\nu_1 \in \mathbb{R}_+$

(ii) *Technicality criterion* P_{10} *holds i.e.*

$$f_{w\mu}(\overline{w},\overline{z};\nu_1) - \eta f_{z\mu}(\overline{w},\overline{z};\nu_1) > 0$$

(iii) $\lambda_1 = B_1'(\overline{x}_1) - D_1'(\overline{x}_1) < 0$

$\lambda_2 = B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) < 0.$

Then Hopf bifurcation occurs at $\mu = \nu_1$ *for the equilibrium* $\mathbf{E}_1(\overline{x}_1, 0, \overline{w}, \overline{z})$ *for system* (3.62).

□

Theorem 3.19. *There is a Hopf bifurcation for system* (3.62) *as* μ *passes through* $\mu = \nu_1$ *emanating from the steady state* $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *leading to periodic solutions for either* $\mu_1 > \nu_1$ *(super-critical bifurcation), or* $\mu < \nu_1$ *(sub-critical-bifurcation) or at* $\mu = \nu_1$.

□

Now, consider the steady state $E_3[x_1^*, x_2^*, w^*, z^*]$. The Jacobian matrix corresponding to $S_\mu = E[x_1^*, x_2^*, w^*, z^*, \mu]$ is given by

newpage $J_\mu(S_\mu) =$

$$= \begin{bmatrix} B_1'(x_1) - D_1'(x_1) \\ -x_2 q_1(x_1, x_2) \\ -x_1 x_2 q_{1,x_1}(x_1, x_2) & -x_1 q_1(x_1, x_2) \\ & -x_1 x_2 q_{1,x_2}(x_1, x_2) & 0 & 0 \\ & B_2'(x_2) - D_2'(x_2(x_2) \\ -x_2 q_2(x_1, x_2) & -x_1 q_2(x_1, x_2) \\ -x_1 x_2 q_{2,x_1}(x_1, x_2) & -x_1 x_2 q_{2,x_2}(x_1, x_2) & -h_w(x_2, w) & 0 \\ & -h_{x_2}(x_2, w) \\ & & f_w(w, t) \\ 0 & -\beta h_{x_2}(x_2, w) & -\alpha_1 e_1'(w) & f_z(w, \mu, z) \\ & & -\beta h_w(x_2, w) \\ & & & -e_2'(z) \\ 0 & 0 & -\eta f_w(w, \mu, z) & -\eta f_z(w, \mu, t) \end{bmatrix}$$

$$= \begin{bmatrix} a_{11}^* & a_{12}^* & 0 & 0 \\ a_{21}^* & a_{22}^* & a_{23}^* & 0 \\ 0 & a_{23}^* & a_{33}^* & a_{34}^* \\ 0 & 0 & a_{43}^* & a_{44}^* \end{bmatrix}. \tag{3.70}$$

The characteristic equation corresponding to $J_\mu(S_\mu)$ is given by

$$\rho(\lambda, J_\mu(S_\mu)) = \det |J_\mu(P_2) - \lambda I_4| = 0$$

$$\Longrightarrow \lambda^4 + a_1^*\lambda^3 + a_2^*\lambda^2 + a_3^*\lambda + a_4^* = 0.$$

In particular, the a_i^*, $i = 1, 2, 3, 4$ are given by

$$a_1^* = -(a_{11}^* + a_{22}^* + a_{33}^* + a_{44}^*)$$

$$a_2^* = \left\{ \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{12}^* \\ \frac{1}{2}a_{12}^* & a_{22}^* \end{vmatrix} + \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{13}^* \\ \frac{1}{2}a_{13}^* & a_{33}^* \end{vmatrix} + \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{14}^* \\ \frac{1}{2}a_{14}^* & a_{44}^* \end{vmatrix} \right.$$
$$\left. + \det \begin{vmatrix} a_{22}^* & \frac{1}{2}a_{23}^* \\ \frac{1}{2}a_{23}^* & a_{33}^* \end{vmatrix} + \det \begin{vmatrix} a_{22}^* & \frac{1}{2}a_{24}^* \\ \frac{1}{2}a_{24}^* & a_{44}^* \end{vmatrix} + \det \begin{vmatrix} a_{33}^* & \frac{1}{2}a_{34}^* \\ \frac{1}{2}a_{34}^* & a_{44}^* \end{vmatrix} \right\}$$

$$a_3^* = -\left\{ \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{12}^* & \frac{1}{2}a_{13}^* \\ \frac{1}{2}a_{12}^* & a_{22}^* & \frac{1}{2}a_{23}^* \\ \frac{1}{2}a_{13}^* & \frac{1}{2}a_{23}^* & a_{33}^* \end{vmatrix} + \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{12}^* & \frac{1}{2}a_{14}^* \\ \frac{1}{2}a_{21}^* & a_{22}^* & \frac{1}{2}a_{24}^* \\ \frac{1}{2}a_{14}^* & \frac{1}{2}a_{24}^* & a_{44}^* \end{vmatrix} \right.$$
$$\left. + \det \begin{vmatrix} a_{11}^* & \frac{1}{2}a_{13}^* & \frac{1}{2}a_{14}^* \\ \frac{1}{2}a_{13}^* & a_{33}^* & \frac{1}{2}a_{34}^* \\ \frac{1}{2}a_{14}^* & \frac{1}{2}a_{43}^* & a_{44}^* \end{vmatrix} + \det \begin{vmatrix} a_{22}^* & \frac{1}{2}a_{23}^* & \frac{1}{2}a_{24}^* \\ \frac{1}{2}a_{23}^* & a_{33}^* & \frac{1}{2}a_{34}^* \\ \frac{1}{2}a_{24}^* & \frac{1}{2}a_{43}^* & a_{44}^* \end{vmatrix} \right\}$$

$$a_4^* = \det J_\mu(S_\mu). \tag{3.71}$$

By the Routh-Hurwitz criteria, necessary and sufficient conditions for all the

roots of $p(\lambda, J_\mu(S_\mu)) = 0$ to have negative real parts are

$$R_1.\quad a_1^* > 0, \quad a_3^* > 0, \quad a_4^* > 0$$

$$\text{and} \quad R_2.\quad a_1^* a_2^* a_3^* > (a_3^*)^2 + (a_1^*)^2 a_4^*.$$

Now in order to have Hopf bifurcation, we must violate either R_1 and R_2.

P_{11}. Suppose each $a_i > 0$ for $i = 1, 2, 3, 4$ such that

(i) $a_2^* a_3^* - a_4^* > 0$ and

(ii) R_2 is violated such that

$$a_1^* a_2^* a_3^* = (a_3^*)^2 + (a_1^*)^2 a_4^*$$

$$\iff a_2^* a_3^* = \frac{(a_3^*)^2}{a_1^*} + a_1^* a_4^* > a_4^*. \tag{3.72}$$

Lemma 3.5. *Let*

(i) *Each* $a_i > 0$ *for* $i = 1, 2, 3, 4$.

(ii) $a_2^* a_3^* - a_4^* > 0$

(iii) *condition* R_2 *be violated.*

Then $\rho(\lambda, J_\mu(S_\mu)) = 0$ *can be factored into the form*

$$(\lambda^2 + k_1)(\lambda + k_2)(\lambda + k_3), \quad k_i > 0, \quad i = 1, 2, 3, 4$$

where

$$\left.\begin{aligned} a_1^* &= k_2k_3 \\ a_2^* &= k_2k_3 + k_1 \\ a_3^* &= k_1(k_2 + k_3) \\ \Longleftrightarrow k_1 &= \tfrac{a_4^*}{a_1^*}, \quad k_2 = \tfrac{a_1^*(a_2^*a_3^* - a_4^*)}{a_2^*a_4^*} \\ k_3 &= \tfrac{a_1^*a_4^*}{a_2^*a^*3 - a_4^*}. \end{aligned}\right\} \tag{3.73}$$

In particular, the spectrum of $J_\mu(S_\mu)$ *is given by*

$$\sigma(J_\mu(S_\mu)) = \{i\sqrt{k_1}, \quad -i\sqrt{k_1}, \quad -k_2, -k_3\} \tag{3.74}$$

□

Thus under the conditions of the lemma, $\rho(\lambda, J_\mu(S_\mu))$ has two pure imaginary roots for some value of μ say $\mu = \nu_2$.

For $\mu \in (\nu_2 - \varepsilon, \nu_2 + \varepsilon)$, the characteristic equation $\rho(\lambda, J_\mu(S_\mu))$ cannot have real positive roots.

But for $\mu \in (\nu_2 - \varepsilon, \nu_2 + \varepsilon)$, the roots are in general of the form

$$\left.\begin{aligned} \lambda_1(\mu) &= \alpha(\mu) + i\beta(\mu) \\ \lambda_2(\mu) &= \alpha(\mu) - i\beta(\mu) \\ \lambda_3(\mu) &= -k_2 \neq 0 \\ \lambda_4(\mu) &= -k_3 \neq 0. \end{aligned}\right\} \tag{3.75}$$

We now apply Hopf's transversality criterion to $\rho(\lambda, J_\mu(S_\mu))$ in order to obtain the required conditions for Hopf bifurcation to occur for this system. Hopf's

transversality criterion [cf. Theorem 1.5, Chapter 1.0] is given by

$$\text{Re}\left[\frac{d\lambda_j}{d\mu}\right]_{\mu=\nu_2} \neq 0 \quad \text{for} \quad j = 1, 2. \tag{3.76}$$

Now substituting $\lambda_j(\mu) = a(\mu) + i\beta(\mu)$ into

$$\rho(\lambda, J_\mu(P_2)) = \lambda^4 + a_1^*\lambda^3 + a_2^*\lambda^2 + a_3^*\lambda + a_4^* = 0 \tag{3.77}$$

and computing the derivatives with respect to μ, we obtain:

$$\left.\begin{aligned}
&\alpha'[\alpha(\alpha^2-\beta^2) - 2\alpha\beta^2] + i4\alpha'[\beta(\alpha^2-\beta^2) + 2\alpha^2\beta] \\
&\quad -4\beta'[\beta(\alpha^2-\beta^2) + 2\alpha^2\beta] + i4\beta'[\alpha(\alpha^2-\beta^2) - 2\alpha\beta^2] \\
&\quad +a_1'[\alpha(\alpha^2-\beta^2) - 2\alpha\beta^2] + ia_1'[\beta(\alpha^2-\beta^2) + 2\alpha^2\beta] \\
&\quad +3\alpha' a_1(\alpha^2-\beta^2) + i\alpha' 6a_1\alpha\beta \\
&\quad -6\beta'\alpha\beta a_1 + i3a_1\beta'(\alpha^2-\beta^2) \\
&\quad +a_2'(\alpha^2-\beta^2) + i2\alpha\beta a_2' + 2a_2\alpha\alpha' + i2a_2\alpha'\beta \\
&\quad -\beta' a_2 2\beta + i2a_2\alpha\beta' + \alpha a_3' + i\beta a_3' \\
&\quad +\alpha' a_3 + ia_3\beta' + a_4' = 0.
\end{aligned}\right\} \tag{3.78}$$

Comparing the real and imaginary parts we have

$$\begin{aligned}
A(\mu)\alpha'(\mu) - B(\mu)\beta'(\mu) + C(\mu) &= 0 \\
B(\mu)\alpha'(\mu) + A(\mu)\beta'(\mu) + D(\mu) &= 0
\end{aligned} \tag{3.79}$$

where

$$A(\mu) = 4\alpha(\alpha^2-\beta^2) - 8\alpha\beta^2 + 3a_1(\alpha^2-\beta^2) + 2a_2\alpha + a_2$$

$$B(\mu) = 4\beta(\alpha^2-\beta^2) + 8\alpha^2\beta + 6\alpha\beta a_1 + 2a_2\beta$$

$$C(\mu) = a_1'[\alpha(\alpha^2 - \beta^2) - 2\alpha\beta^2] + a_2'(\alpha^2 - \beta^2) + \alpha a_3' + a_4'$$

$$D(\mu) = a_1'[\beta(\alpha^2 - \beta^2) + 2\alpha^2\beta] + 2\alpha\beta a_2' + \beta a_3'.$$

Thus

$$\begin{aligned} \mathrm{Re}\left[\frac{d\lambda_j}{d\mu}\right]_{\mu=\nu_2} &= \alpha'(\nu_2) \\ &= \frac{\det \begin{vmatrix} -C(\mu) & -B(\mu) \\ -D(\mu) & A(\mu) \end{vmatrix}}{\det \begin{vmatrix} A(\mu) & -B(\mu) \\ B(\mu) & A(\mu) \end{vmatrix}_{\mu=\nu_2}} \\ &= -\frac{(AC+BD)}{A^2+B^2}\Big|_{\mu=\nu_2} \neq 0, \end{aligned} \tag{3.80}$$

since

$$A(\nu_2)C(\nu_2) + B(\nu_2)D(\nu_2) \neq 0. \tag{3.81}$$

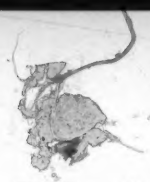
Theorem 3.20. *Suppose*

(i) *System* (3.22) *is uniformly persistent.*

(ii) $E^* = [x_1^*, x_2^*, w^*, z^*]$ *exists.*

(iii) *Lemma* 4.0 *holds.*

Then system 3.22 *exhibits a (small amplitude) Hopf-Andronov-Poincaré bifurcation in the first orthant, leading to a family of periodic solutions that bifurcate*



from E^* *for suitable values of* μ *in the neighborhood of* $\mu = \nu_2$.

□

Remark 3.5. It has been established that system (3.0) has solutions which are eventually bounded in the future. Also the equilibrium $E_2[0, x_2, w, z]$ is constrained as a hyperbolic saddle point. Furthermore, Theorems 3.19 and 3.20 establish $\mu = \nu_1$ and $\mu = \nu_2$ as two bifurcation values. In particular, a periodic solution bifurcates from $E_1[x_1, 0, w, z]$ when μ passes through ν_1. We denote $S_1 = [x_1(t, \nu_1), x_2(t, \nu_1), w(t, \nu_1), z(t, \nu_1)]$. Another periodic solution $S_2 = [x_2(t, \nu_2), x_2(t, \nu_2), w(t, \nu_2), z(t, \nu_2)]$ bifurcates from E^* when μ passing through ν_2.

Theorems 3.16 - 3.21 imply that during adoptive cancer immunotherapy as described in this chapter, it is possible under the specified criteria, that Hopf bifurcations occurs from the clinically preferred steady state $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ leading to periodic orbits. This phenomenon complicates the nature and outcome of therapy as a second subsequent bifurcation may lead to periodic orbits near the less preferred rest point $E^*[x_1^*, x_2^*, w^*, z^*]$.

Remark 3.6. Theorems 3.14 and 3.15 imply that the normal cells and cancer cells persist under continuous infusion of LAK cells and interleukin-2. Thus the therapy is unable to annihilate the cancer cells but is able to control the lethal proliferation of the cancer cells.

If the cancer cell number during therapy is either below the detection threshold of 10^9 cells or the subclinical threshold of 10^3 cells, then the outcome of

the therapy may be declared a 'partial' therapeutic success. The only problem associated with this result is that therapy must be continued indefinately and the cancer cell number must be preferably subclinical.

However the much preferred objective of cancer immunotherapy is the total annihilation of the cancer cells. This will require that the rest point $E_1[\overline{x}_1, 0, \overline{w}, z]$ be globally asymptotically stable with respect to solutions initiating from int $\mathbb{R}_{x_1 x_2 w z}$. The required criteria for this condition of 'total cure', will be established in the next section.

□

3.9. Criteria for a 'Total Cure'

In this section, necessary and sufficient criteria for total or absolute elimination of all cancer cells will be derived. Usually during cancer therapy the time domain of therapeutic efficacy of the anti-cancer drug is very restricted and the cancer cells eventually repopulate leading to the death of the patient. In such scenarios, the rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ is locally asymptotically stable during therapy and eventually becomes unstable during the repopulation of cancer cells.

In order to obtain the conditions for 'total cure', we must, by means of a Liapunov function, establish criteria for *global* asymptotic stability of the rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$.

3.6.1. Global asymptotic stability of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ with respect to $\overline{\mathbb{R}}^+_{x_1 x_2 w z}$.

We choose the Liapunov function

$$V = x_1 - \overline{x}_1 - x_1 \ell n \left(\frac{x_1}{\overline{x}_1} \right) + k_1 x_2 + \frac{1}{2} k_2 (w - \overline{w})^2 + \frac{1}{2} k_3 (z - \overline{z})^2. \qquad (3.83)$$

The derivative of (3.83) along the solution trajectories of (3.0) and using (3.45) leads to the following algebraic equations:

$$\begin{aligned} \dot{V} = & (x_1 - \overline{x}_1)[g_1(x_1) - x_2 q_1(x_1, x_2)] \\ & + k_1 x_2 [g_2(x_2) - x_1 q_2(x_1, x_2) - h_1(x_2, w)] \\ & + k_2 (w - \overline{w})[Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w)] \\ & + k_3 (z - \overline{z})[Q_2 - \alpha_2 e_2(z) - \eta f(w, z)]. \end{aligned} \qquad (3.84)$$

$$\begin{aligned} \dot{V} = & (x_1 - \overline{x}_1) g_1(x_1) - (x_1 - \overline{x}_1) x_2 q_1(x_1, x_2) \\ & + k_1 x_2 [g_2(x_2) - \widehat{x}_1 q_2(\widehat{x}_1, x_2) - k_1 x_2 [w h_2(x_2, w) - \overline{w} h_2(x_2, \overline{w})] \\ & - k_1 x_2 \overline{w} h_2(x_2, \overline{w}) \\ & + \alpha_1 k_2 (w - \overline{s})[e_1(\overline{w}) - e_1(w)] + k_2 (w - \overline{w})[f(w, z) - f(\overline{w}, \overline{z})] \\ & - \beta k_2 (w - \overline{w}) x_2 [w h_2(x_2, w) - \overline{w} h_2(x_2, \overline{w})] - \beta k_2 (w - \overline{w}) x_2 h_2(x_2, \overline{w}) \\ & + \alpha_2 k_3 (z - \overline{z})[e_2(\overline{z}) - e_2(z)] + \eta k_3 (z - \overline{z})[f(\overline{w}, \overline{z}) - f(w, z)]. \end{aligned} \qquad (3.85)$$

Now

$$\dot{V} = X^T D X \tag{3.86}$$

where

$$X = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} x_1 - \overline{x}_1 \\ x_2 \\ w - \overline{w} \\ z - \overline{z} \end{pmatrix}$$

and D is a real symmetric matrix such that

$$D = \{d_{ij}\}_{1 \le i,j \le 4}$$

and

$$d_{11} = \frac{g_1(x_1)}{(x_1 - \overline{x}_1)}$$

$$d_{12} = -q_1(x_1, x_2)$$

$$d_{13} = 0$$

$$d_{14} = 0$$

$$d_{22} = \frac{[g(x_2) - \overline{x}_1 q_2(\overline{x}_1, x_2)] - k_1 \overline{w} h_2(x_2, \overline{w})}{x_2}$$

$$d_{23} = \frac{-k_1[w h_2(x_2, w) - \overline{w} h_2(x_2, \overline{w})]}{(w - \overline{w})} - \beta k_2 h_2(x_2, \overline{w}) - \beta k_2[w h_2(x_2, w) - \overline{w} h_2(x_2, \overline{w})]$$

$$d_{33} = -\alpha_1 k_2[e_1(w) - e_1(\overline{w})]$$

$$d_{34} = \frac{k_2[f(w,z) - f(\overline{w},\overline{z})]}{z - \overline{z}} - \eta k_3 \frac{[f(w,z) - f(\overline{w},\overline{z})]}{(w - \overline{w})}$$

$$d_{44} = -\alpha_2 k_3[e_2(z) - e_2(\overline{z})]. \tag{3.87}$$

The explicit form of matrix D is as given by (3.88).

$$D = \begin{pmatrix} d_{11} & \frac{1}{2}d_{12} & \frac{1}{2}d_{13} & \frac{1}{2}d_{14} \\ \frac{1}{2}d_{12} & d_{22} & \frac{1}{2}d_{23} & \frac{1}{2}d_{24} \\ \frac{1}{2}d_{13} & \frac{1}{2}d_{23} & d_{33} & \frac{1}{2}d_{34} \\ \frac{1}{2}d_{14} & \frac{1}{2}d_{24} & \frac{d}{1}2d_{34} & d_{44} \end{pmatrix}. \tag{3.88}$$

Theorem 3.21. *The matrix D and consequently the quadratic form* (3.86) *is negative definite if the following criteria hold:*

$$\begin{aligned} D_1 &= d_{11} < 0, \\ D_2 &= \det \begin{vmatrix} d_{11} & \frac{1}{2}d_{12} \\ \frac{1}{2}d_{12} & d_{22} \end{vmatrix} > 0 \\ D_3 &= \det \begin{vmatrix} d_{11} & \frac{1}{2}d_{12} & \frac{1}{2}d_{13} \\ \frac{1}{2}d_{12} & d_{22} & \frac{1}{2}d_{23} \\ \frac{1}{2}d_{13} & \frac{1}{2}d_{23} & d_{33} \end{vmatrix} < 0 \\ D_4 &= \det \begin{vmatrix} d_{11} & \frac{1}{2}d_{12} & \frac{1}{2}d_{13} & \frac{1}{2}d_{14} \\ \frac{1}{2}d_{12} & d_{22} & \frac{1}{2}d_{23} & \frac{1}{2}d_{24} \\ \frac{1}{2}d_{13} & \frac{1}{2}d_{23} & d_{33} & \frac{1}{2}d_{34} \\ \frac{1}{2}d_{14} & \frac{1}{2}d_{24} & \frac{1}{2}d_{34} & d_{44} \end{vmatrix} > 0. \end{aligned} \tag{3.89}$$

Proof. The proof follows directly from Frobenius' Theorem, and the Hermiticity of D.

We then have the following theorem:

Theorem 3.22. *Let $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ denote the cancer-free equilibrium for the*

cancer immunotherapy system (3.0). *Then* $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *is globally asymptotically stable or equivalently, there is total annihilation of the cancer cells, if conditions* (3.89) *of Theorem* 3.21 *are satisfied.*

□

Remark 3.7. If the persistence criteria specified in Theorems 3.14 and 3.15 are violated, then either the cancer cells or normal cells, but most likely the normal cells of the afflicted organ, will be outcompeted and annihilated by the cancer cells, if the therapy is ineffective.

It is possible also, that the normal cell density in the organ may fluctuate periodically or chaotically before eventual extinction, according to the principles of Dynamical Disease as mentioned in the introduction.

On the other hand if the adoptively transferred lymphocytes (LAK cells) and lymphokines (IL-2) are very potent and therapeutically efficacious, then the cancer cells may be driven to extinction if persistence fails.

□

Criteria for extinction of normal cells

In this subsection, we shall derive sufficient conditions for the extinction of the normal cells in the afflicted anatomical organ and in the case of extinction, the probable consequent death of the cancer patient. This will be done by using a Liapunov function to provide criteria for the rest point $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ to be

globally asymptotically stable and hence unique. We choose the Liapunov function V as given by (3.90):

$$V = c_1 x_1 + x_2 - \hat{x}_2 - x_2 \ell n \frac{x_2}{\hat{x}_2} + \frac{1}{2} c_2 (w - \hat{w})^2 + \frac{1}{2} c_3 (z - \hat{z})^2. \tag{3.90}$$

The derivative of (3,90) along the solution curves of (3.0) is given by the equation:

$$\dot{V} = c_1 \dot{z}_1 + \frac{(x_1 - \hat{x}_2)}{x_2} \dot{x}_2 + c_2 (w - \hat{w}) \dot{w} + c_3 (z - \hat{z}) \dot{z} \tag{3.91}$$

$$\begin{aligned} &= c_1 x_1 [g_1(x_1) - x_2 q_1(x_1, x_2)] \\ &\quad + (x_2 - \hat{x}_2)[g_2(x_2) - x_1 q_1(x_1, x_2) - h_1(x_2, w)] \\ &\quad + c_2 (w - \hat{w})[Q_1 - \alpha_1 e_1(w) + f(w, z) - \beta h(x_2, w)] \\ &\quad + c_3 (z - \hat{z})[Q_2 - \alpha_2 e_2(z) - \eta f(w, z)]. \end{aligned} \tag{3.92}$$

We then use (3.45) and the equilibrium algebraic expressions and tacit rearrangement to obtain a modified form of $\dot{V}$ as follows:

$$\begin{aligned} \dot{V} &= c_1 x_1 g_1(x_1) - c_1 x_1 [x_2 q_1(x_1, x_2) - \hat{x}_2 q_1(x_1, \hat{x}_2)] - c_1 x_1 \hat{x}_2 q_1(x_1, \hat{x}_2) \\ &\quad + (x_1 - \hat{x}_2) g_2(x_2) - (x_2 - \hat{x}_2) x_1 q_1(x_1, x_2) \\ &\quad - (x_2 - \hat{x}_2)[w h_2(x_2, w) - \hat{w} h_2(x_2, \hat{w})] - (x_2 - \hat{x}_2) \hat{w} h_2(x_2, \hat{w}) \\ &\quad + c_2 (w - \hat{w}) \alpha_1 [e_1(\hat{w}) - e_1(w)] + c_2 (w - \hat{w}) \beta [h(\hat{x}_1, \hat{w}) - h(x_2, w)] \\ &\quad + c_2 (w - \hat{w})[f(w, z) - f(\hat{w}, \hat{z})] \end{aligned}$$

$$+ c_3(z-\hat{z})\alpha_2[e_2(\hat{z}) - e_2(z)] + c_3(z-\hat{z})\eta[f(\hat{w},\hat{z}) - f(w,z)]. \tag{3.93}$$

Now

$$\dot{V} = X^T E X \tag{3.94}$$

where

$$X = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} x_1 \\ x_2 - \hat{x}_2 \\ w - \hat{w} \\ z - \hat{z} \end{pmatrix}.$$

E is a symmetric 4×4 matrix over IR and $E = \{e_{ij}\}_{1 \le i,j \le 4}$ with

$$E = \begin{pmatrix} e_{11} & \frac{1}{2}e_{12} & \frac{1}{2}e_{13} & \frac{1}{2}e_{14} \\ \frac{1}{2}e_{12} & e_{22} & \frac{1}{2}e_{23} & \frac{1}{2}e_{24} \\ \frac{1}{2}e_{13} & \frac{1}{2}e_{23} & e_{33} & \frac{1}{2}e_{34} \\ \frac{1}{2}e_{14} & \frac{1}{2}e_{24} & \frac{1}{2}e_{34} & e_{44} \end{pmatrix}, \tag{3.95}$$

and

$$\begin{aligned} \dot{V} = {} & e_{11}v_1^2 + e_{12}v_1v_2 + e_{13}v_1v_3 + e_{14}v_1v_4 \\ & + e_{22}v_2^2 + e_{23}v_2v_3 + e_{24}v_2v_4 + e_{33}v_3^2 \\ & + e_{34}v_3v_4 + e_{44}v_4^2, \end{aligned}$$

where

$$e_{11} = \frac{c_1[g_1(x_1) - \hat{x}_2 q_1(x_1, \hat{x}_2)]}{x_1}$$

$$e_{12} = \frac{-c_1[x_2 q_1(x_1, x_2) - \hat{x}_2 q_1(x_1, \hat{x}_2)]}{(x_2 - \hat{x}_2)} - q_1(x_1, x_2)$$

$$e_{13} = 0$$

$$e_{22} = \frac{[g_2(x_2) - \widehat{w}h_2(x_2, \widehat{w})]}{(x + 2 - \widehat{x}_2)}$$

$$e_{23} = \frac{[wh_2(x_2, w) - \widehat{w}h_2(x_2, \widehat{w})]}{(w - \widehat{w})} + c_2\beta \frac{[h(\widehat{x}_2, \widehat{w}) - h(x_2, w)]}{(x_2 - \widehat{x}_2)}$$

$$e_{33} = \frac{-c_2\alpha_1[e_1(w) - e_1(\widehat{w})}{(w - \widehat{w})}$$

$$e_{34} = \frac{c_2[f(w, z) - f(\widehat{w}, \widehat{z})]}{(z - \widehat{z})} - c_3\eta \frac{[f(w, z) - f(\widehat{w}, \widehat{z})]}{(w - \widehat{w})}$$

$$e_{44} = -\frac{c_3\alpha_2[e_2(z) - e_2(\widehat{z})]}{(z - \widehat{z})}. \tag{3.96}$$

Theorem 3.23. *The real symmetric matrix E and consequently the quadratic form (3.94) is negative definite if the following criteria hold for the leading principal minor matrices E_i, $i = \{1, 2, 3, 4\}$:*

$$E_1 = e_{11} < 0$$

$$E_2 = \det \begin{vmatrix} e_{11} & \frac{1}{2}e_{12} \\ \frac{1}{2}e_{12} & e_{22} \end{vmatrix} > 0$$

$$E_3 = \det \begin{vmatrix} e_{11} & \frac{1}{2}e_{12} & \frac{1}{2}e_{13} \\ \frac{1}{2}e_{12} & e_{22} & \frac{1}{2}e_{23} \\ \frac{1}{2}e_{13} & \frac{1}{2}e_{23} & e_{33} \end{vmatrix} < 0$$

$$E_4 = \det \begin{vmatrix} e_{11} & \frac{1}{2}e_{12} & \frac{1}{2}e_{13} & \frac{1}{2}e_{14} \\ \frac{1}{2}e_{12} & e_{22} & \frac{1}{2}e_{23} & \frac{1}{2}e_{24} \\ \frac{1}{2}e_{13} & \frac{1}{2}e_{23} & e_{33}\frac{1}{2}e_{34} & \\ \frac{1}{2}e_{14} & \frac{1}{2}e_{24} & \frac{1}{2}e_{34} & \frac{1}{2}e_{44} \end{vmatrix} > 0. \tag{3.97}$$

Proof. The proof follows directly from the Frobenius Theorem and the fact that E is a real symmetric matrix and consequently Hermitian $[E = (E^*)^T]$.

□

The results of the preceding theorem leads to the following theorem which is the manifestation of therapeutic failure of the anti-cancer immunotherapy drugs (LAK and IL-2).

Theorem 3.24. *Suppose the criteria* (3.97) *of Theorem* 3.23 *hold. Then clinically the cancer immunotherapy drug protocol will be strongly non-efficacious and eventually the normal cells in the afflicted organ will be annihilated, leading to probable death of the cancer patient.*

□

Remark 3.8. During the clinical administration of LAK and IL-2, it is therapeutically prudent to use continuous infusions *interspaced* with days of no infusions [cf. 28]. This will enable the patient's physiological system to recover from drug toxicities and associated "therapeutic stress". The advantages of such procedure may be circumvented by the phenomenon of repopulations of the tumor by drug-resistant cancer cells. In the next subsection, we shall analyse the local stability of periodic infusion of LAK and IL-2. The phenomenom of drug resistance and optimal therapy policies will not be addressed in this thesis but deferred to future research.

Periodic treatment case

We now consider the treatment scenario in which the LAK and IL-2 are given by periodic adoptive transfusions. The input functions $Q_1(t)$ and $Q_2(t)$ are in the form of Heaviside-type step functions with equal or unequal dose rates of period w.

Let $\mathbb{B}_w$ be the Banach space of real valued, continuous ω-periodic functions of a real variable t.

Consider the periodic system

$$\left.\begin{aligned}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) \\
\dot{x}_2 &= B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - h(x_2, w) \\
\dot{w} &= Q_1(t) - \alpha_1 e(w) + f(w, z) - \beta h(x_2, w) \\
\dot{z} &= Q_2(t) - \alpha_2 e_2(z) - \eta f(w, z) \\
Q_1(t) &= Q_1(t+\omega) \\
Q_2(t) &= Q_2(t+\omega) \\
x_1(t_0) &= x_{10} \\
x_2(t_0) &= x_{20} \\
w(t_0) &= w_0 \\
z(t_0) &= z_0.
\end{aligned}\right\} \qquad (3.98)$$

We make the following assumptions:

a1. $Q_1, Q_2 \in \mathbb{B}'_\omega$

a2. The system (3.98) in $\overline{\mathbb{R}}^+_{x_1 w z}$, has a positive ω-periodic solution Φ such

that

$$0 < \Phi = \Phi_0 = (\widetilde{x}_1, \widetilde{w}, \widetilde{z}) \in \mathbb{B}^3_w.$$

a3. Let Ω^4 denote an open set in $\mathbb{R}^4_+$. Then $(0, \Phi_0) \in \Omega^4$ for all $t \in [0, \infty)$.

The assumptions a1 - a3 imply the existence of a non-trivial ω-periodic solution $(x_2, \Phi) = (0, \Phi_0)$ on the boundary of the positive cone in $\mathbb{B}_w \times \mathbb{B}^3_w$.

a4. The solution $\Phi = \Phi_0$ is such that Φ_0 is non-critical. This implies that all the Floquet exponents of the linearization of (3.98) in $\overline{\mathbb{R}}^{+}_{x_1 wz}$ in the neighborhood of Φ_0 have non-zero real parts.

a5. System (3.98) satisfies the invariance of non-negativity criteria.

Let us define $\Omega^4_w(\Phi_0)$ as follows:

$$\Omega^4_w(\Phi_0) = \{(x_2, \Phi) \in \mathbb{B}_w \times \mathbb{B}^3_w | (x_2(t), \Phi(t) + \Phi_0(t)) \in \Omega^4 \text{ for all } t\}. \qquad (3.99)$$

The assumption a5 implies that $\Omega^4_w(\Phi_0)$ is an open set in $\mathbb{B}_w \times \mathbb{B}^3_w$ which contains $(0, \Phi_0(t))$.

The Jacobian matrix due to linearization of (3.98) in the neighborhood of the periodic orbit $(0, \Phi_0(t))$ is given by the expression

$$J(0,\Phi_0)=\begin{bmatrix} B_1'(\widetilde{x}_1)-D_1'(\widetilde{x}_1) & -\widetilde{x}_1 q_1(\widetilde{x}_1,0) & 0 & 0 \\ 0 & B_2'(0)-D_2'(0)-\widetilde{x}_1 q_2(\widetilde{x}_1,0)-h_{x_2}(0,\widetilde{w}) & 0 & 0 \\ 0 & -\beta h_{x_2}(0,\widetilde{w}) & f_w(\widetilde{w},\widetilde{z})-\alpha_1 e_1'(\widetilde{w}) & f_z(\widetilde{w},\widetilde{z}) \\ 0 & 0 & -\eta f_w(\widetilde{w},\widetilde{z}) & -\alpha_2 e_2'(\widetilde{z})-\eta f_z(\widetilde{w},\widetilde{z}) \end{bmatrix} \tag{3.100}$$

In computing $J(0,\Phi_0)$ we made use of assumption a2. Note that

$$\Phi_0 = \Phi_0(t) = (\widetilde{x}_1(t), \widetilde{w}(t), \widetilde{z}(t)).$$

Let the Floquet multipliers of (3.100) be $\rho_i, \quad i=\{1,2,3,4\}$. Then,

$$\begin{aligned} \rho_1 &= e^{\int_0^\omega B_1'(\widetilde{x}_1(s))-D_1'(\widetilde{x}_1(s))} \\ \rho_2 &= e^{\int_0^\omega B_2'(0)-D_2'(0)-\widetilde{x}_1 q_2(\widetilde{x}_1,0)-h_{x_2}(0,\widetilde{w})} \end{aligned} \tag{3.101}$$

and ρ_3, ρ_4 are Floquet multipliers of the matrix

$$\begin{aligned} M(t) &= \begin{pmatrix} f_w(\widetilde{w},\widetilde{z})-\alpha_1 e_1'(\widetilde{w}) & f_z(\widetilde{w},\widetilde{z}) \\ -\eta f_w(\widetilde{w},\widetilde{z}) & -\alpha_2 e_2'(\widetilde{w})-\eta f_z(\widetilde{w},\widetilde{z}) \end{pmatrix} \\ &= \{\widetilde{m}_{ij}(t)\}_{1\le i,j\le 2}\,. \end{aligned} \tag{3.102}$$

In particular, the matrix (3.101) corresponds to the Jacobian matrix of linearization of (3.98) in $\overline{\mathbb{R}}^+_{wz}$ in the neighborhood of $(\widetilde{w}(t),\widetilde{z}(t))$.

We define the following with respect to the matrix $M(t)$:

$$\|x\| = \sup_k |x_k|$$

$$\|M(t)\| = \sup_k \sum |m_{ik}|$$

$$\mu(M(t)) = \sup_k \left\{ \text{Re } m_{kk} + \sum_{i,k \neq i} |m_{ik}| \right\}. \tag{3.103}$$

The Lozinski matrix measure of $M(t)$ takes the simplified form

$$\mu(M(t)) = \sup \{m_{11} + |m_{21}|,\ m_{22} + |m_{12}|\}.$$

Theorem 3.25. *Let*

$$\hat{\mu}(t) \triangleq \max \{(\eta + 1) f_w(\tilde{w}(t), \tilde{z}(t)) - \alpha_1 e_1'(\tilde{w}(t)),$$

$$(1 - \eta) f_z(\tilde{w}(t), \tilde{z}(t)) - \alpha_2 e_2'(\tilde{z}(t))\} \tag{3.104}$$

where $(\tilde{w}(t), \tilde{z}(t))$ *is the periodic orbit specified by assumption* a2.

If $\hat{\mu}(M(t)) \leq -\alpha$, $\alpha > 0$, *then* $(\tilde{w}(t), \tilde{z}(t))$ *is uniformly asymptotically stable and consequently the Floquet multipliers* ρ_3, ρ_4 *of* $M(t)$, *are such that* $|\rho_i| < 1$, $i = 3, 4$.

Proof. The function $\hat{\mu}(M(t))$ defined by (3.104) is the simplified form of the Lozinskii matrix measure $\mu(M(t))$. The theorem therefore follows from Lozinskii matrix stability criteria and Floquet theory discussed in Chapter 1.

Remark 3.9. If $\eta > 1$ and $\alpha_1 e_1'(\widetilde{w}(t)) > (\eta+1) f_w(\widetilde{w}(t), \widetilde{z}(t))$, then the α in Theorem 3.25 exists.

Theorem 3.26. *Suppose*

(i) $\int_0^\omega [B_1'(\widetilde{x}_1(s)) - D_1'(\widetilde{x}_1(s))]ds < 0$

(ii) $\int_0^\omega [B_2'(0) - D_2'(0) - \widetilde{x}_1(s) q_2(\widetilde{x}_1(s), 0) - h_{x_2}(0, \widetilde{w}(s))]ds < 0.$

(iii) *The conditions of Theorem* 3.25 *hold.*

Then the periodic solution $(0, \Phi_0(t))$ *is locally uniformly asymptotically stable.*

Proof. The hypotheses (i), (ii) and (iii) imply that $|\rho_i| < 1, \quad i = 1, 2, 3, 4$. Hence the result follows from Floquet theory.

Remark 3.10. Theorem 3.26 conveys the idea that during the periodic adoptive transfer of LAK and IL-2 into the cancer patient, it is possible, in principle, to destroy all the cancer cells within a restricted (finite) time domain of therapeutic efficacy of drug. But on the global time scale, the prospect of a 'total cure' cannot be guaranteed because bifurcations of the periodic orbit $(0, \Phi_0(t))$ may occur, leading to the re-emergence of the cancer as the (interior) periodic branch $(x_2, \Phi(t))$ manifests. This type of bifurcations from periodic orbits have been studied by several authors.

3.10. Examples on Cancer Treatment Using ACI Protocol

In this subsection, we shall use a specific example to illustrate the mathematical principles underlying the therapeutic efficacy of Adoptive Cancer Immunotherapy (ACI). Let us make the following choice for the general functions B_i, D_i, $i=1,2$; $f(w,z)$; $h(x_2,w)$; $e_1(w)$, $e_2(z)$ and $q_i(x_1,x_2)$.

Let the functions be as specified below.

e_1. $B_1(x_1)-D_1(x_1) \triangleq a_{11}x_1 - a_{12}x_1^2$ (a_{ij} are positive constants). This is the logistic function for normal cell growth.

e_2. $B_2(x_2)-D_2(x_2) \triangleq \frac{b_{11}x_2}{1+b_{12}x_2} - b_{22}x_2$.

This is a clinically-based tumor growth model postulated by Piantadosi (1985), Comp. Biomed. Res. 18, page 220. Here, b_{ij} are positive constants.

e_3. $h(x_2,w) \triangleq \frac{b_{24}x_2w}{1+x_2+w}$.

This form of tumoricidal function is discussed by Merril [20].

e_4. $f(w,z) \triangleq \frac{c_{12}wz}{1+z}$, $c_{12}>0$.

This form is chosen by examining the bioclinical data presented in [12,28,19,24].

e_5. $q_i(x_1,x_2) \triangleq \begin{cases} a_{13} & \text{if } i=1 \\ b_{23} & \text{if } i=2. \end{cases}$ where $a_{13}, b_{23} \in \mathbb{R}_+$

$$e_6. \quad \left.\begin{array}{l} e_1(w) = k_1 w \\ e_2(z) = k_2 z \end{array}\right\}, \quad k_1, k_2 \in \mathbb{R}_+ .$$

This drug elimination/degradation is assumed to be linear first order kinetics.

Using the hypotheses $e_1 - e_6$, the cancer immunotherapy system equations (3.0) take the following form:

$$\left.\begin{array}{l} \dot{x}_1 = a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 \\ \dot{x}_2 = \frac{b_{11}x_2}{1+b_{12}x_2} - b_{22}x_2 - b_{23}x_2x_1 - \frac{b_{24}x_2w}{1+x_2+w} \\ \dot{w} = Q_1 - c_{11}w + \frac{c_{12}wz}{1+z} - \frac{c_{13}x_2w}{1+x+2+w} \\ \dot{z} = Q_2 - d_{11}z - \frac{d_{12}wz}{1+z} \\ \text{where} \quad d_{12} = c_{12}\eta, \quad c_{13} = \beta b_{24}, \quad c_{11} = k_1\alpha_1, \\ \qquad d_{11} = k_2\alpha_2 \\ \text{and} \quad x_1(t_0) = x_{10}, \quad x_2(t_0) = x_{20}, \quad w(t_0) = w_0, \quad z(t_0) = z_0. \end{array}\right\} \tag{3.105}$$

The analysis of (3.105) when Q_1, Q_2 are non-periodic

We now discuss system (3.105) under the scenario in which the infusion functions are constant and continuous.

We define the invariant box $\mathbb{IB}$ as follows:

$$\mathbb{IB} = \left\{(x_1, x_2, w, z) \in \mathbb{R}_+^4 \,\middle|\, 0 \le x_1 \le K_1, \quad 0 \le x_2 \le K_2, \right.$$
$$\left. 0 \le w \le -\frac{Q_1}{\delta_1}, \quad 0 \le z \le \frac{Q_2}{\delta_2}\right\}$$

where

$$\left.\begin{array}{ll} \text{(i)} & K_1 = \frac{a_{11}}{a_{12}}, \quad K_2 = \frac{(\frac{b_{11}}{b_{22}} - 1)}{b_{12}} \quad \text{with} \quad \frac{b_{11}}{b_{22}} > 1 \\ \text{(ii)} & \delta_1 = \{c_{12} - c_{11}\} \quad \text{with} \quad c_{12} < c_{11} \\ \text{(iii)} & \delta_2 = d_{11}. \end{array}\right\}. \tag{3.106}$$

By Theorem 3.0, IB is positively invariant and all solutions of (3.105) with initial values in $\overline{\mathbb{R}}^+_+$ are eventually uniformly bounded and are attracted into the region IB.

Let

$$\overline{M}_{22} = \begin{pmatrix} \frac{c_{12}\overline{z}}{1+\overline{z}} - c_{11} & \frac{c_{12}\overline{w}}{(1+\overline{z})^2} \\ -\frac{d_{12}\overline{z}}{1+\overline{z}} & -d_{11} - \frac{d_{12}\overline{w}}{(1+\overline{z})^2} \end{pmatrix}. \tag{3.107}$$

Theorem 3.27. *The clinically desirable rest point* $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *exists uniquely if the following criteria hold:*

(i) *Definitions* (3.106) *hold.*

(ii) $a_{11} > 0$, Trace $\overline{M}_{22} < 0$, *and* det $\overline{M}_{22} > 0$.

Proof. The proof follows directly from Lemma 3.1 and along the same lines as Theorem 3.4. (Note that $(\overline{x}_1, \overline{w}, \overline{z})$ can be explicitly computed by setting the right hand side of (3.105) to zero and solving numerically.)

Remark 3.11. The existence of the rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ is an essential prognicator of a favorable therapeutic outcome. If $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ does not exist, then

the patient is non-responsive to therapy. But the existence must be followed by local as well as global asymptotic stability to spell a much better prognosis for the patient.

Theorem 3.28. *The clinically desired rest point* $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ *is locally asymptotically stable (hyperbolic sink) if the following criteria hold.*

(i) $b_{11} - \overline{x}_1 - \frac{b_{22}\overline{w}}{1+\overline{w}} < 0$

(ii) $a_{11} - 2a_{12}\overline{x}_1 < 0$

(iii) trace $\overline{M}_{22} < 0$ *and* det $\overline{M}_{22} > 0$.

Proof. The proof follows directly from definitions (3.106) and Theorem 3.6.

□

We shall now give necessary and sufficient conditions for the global asymptotic stability of the clinically desired rest point, $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$. These criteria will specify the conditions for a 'total cure' of the cancer – a scenario in which all cancer cells are annihilated.

We choose the Liapunov function V as given by (3.83)

$$V = x_1 - \overline{x}_1 - x_1 \ell n \left(\frac{x_1}{\overline{x}_1}\right) + k_1 x_2 + \frac{1}{2}k_2(w - \overline{w})^2 + \frac{1}{2}k_3(z - \overline{z})^2.$$

Then the derivative of V along the solution curves of (3.105) satisfies equation

(3.108).

$$\dot{V} = X^T \overline{D} X \tag{3.108}$$

where

$$X = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} x_1 - \overline{x}_1 \\ x_2 \\ w - \overline{w} \\ z - \overline{z} \end{pmatrix}$$

and $\overline{D}$ is a real symmetric matrix such that $\overline{D} = \{\overline{d}_{ij}\}_{1 \le i,j \le 4}$ where $\overline{d}_{ij}$ have the following definitions:

$$\overline{d}_{11} = \frac{(a_{11} - a_{12}x_1)}{(x_1 - \overline{x}_1)}$$

$$\overline{d}_{12} = -1$$

$$\overline{d}_{13} = 0$$

$$\overline{d}_{14} = 0$$

$$\overline{d}_{23} = \frac{-k\left[\frac{wc_{13}}{1+x_2+w} - \frac{\overline{w}c_{13}}{1+x_2+\overline{w}}\right]}{(w - \overline{w})} - \frac{\beta k_2 c_{13}}{1 + x_2 + \overline{w}}$$

$$- \beta k_2 \left[\frac{wc_{13}}{1 + x_2 + w} - \frac{\overline{w}c_{13}}{1 + x_2 + \overline{w}}\right]$$

$$\overline{d}_{33} = -\alpha_1 k_2 k_1 [w - \overline{w}]$$

$$\overline{d}_{34} = \frac{k_2\left[\frac{c_{12}wz}{1+z} - \frac{c_{12}\overline{w}\,\overline{z}}{1+\overline{z}}\right]}{(z - \overline{z})} - \frac{\eta k_3\left(\frac{c_{12}wz}{1+z} - \frac{c_{12}\overline{w}\,\overline{z}}{1+\overline{z}}\right]}{(w - \overline{w})}$$

$$\overline{d}_{44} = -\alpha_2 k_3 k_2 [z - \overline{z}]. \tag{3.109}$$

Theorem 3.29. *The clinically desired rest point* $E_1(\overline{x}_1, 0, \overline{w}, \overline{z}]$ *is globally asymp-*

totically stable if the following criteria hold:

(i) $\overline{d}_{11} < 0$

(ii) $$\det \begin{vmatrix} \overline{d}_{11} & \frac{1}{2}\overline{d}_{12} \\ \frac{1}{2}\overline{d}_{12} & \overline{d}_{22} \end{vmatrix} > 0$$

(iii) $$\det \begin{vmatrix} \overline{d}_{11} & \frac{1}{2}\overline{d}_{12} & \frac{1}{2}\overline{d}_{13} \\ \frac{1}{2}\overline{d}_{12} & \overline{d}_{22} & \frac{1}{2}\overline{d}_{23} \\ \frac{1}{2}\overline{d}_{13} & \frac{1}{2}\overline{d}_{23} & \overline{d}_{33} \end{vmatrix} < 0$$

(iv) $$\det \begin{vmatrix} \overline{d}_{11} & \frac{1}{2}\overline{d}_{12} & \frac{1}{2}\overline{d}_{13} & \frac{1}{2}\overline{d}_{14} \\ \frac{1}{2}\overline{d}_{12} & \overline{d}_{22} & \frac{1}{2}\overline{d}_{23} & \frac{1}{2}\overline{d}_{24} \\ \frac{1}{2}\overline{d}_{13} & \frac{1}{2}\overline{d}_{23} & \overline{d}_{33} & \frac{1}{2}\overline{d}_{34} \\ \frac{1}{2}\overline{d}_{14} & \frac{1}{2}\overline{d}_{24} & \frac{1}{2}\overline{d}_{34} & \overline{d}_{44} \end{vmatrix} > 0. \qquad (3.110)$$

Proof. The proof follows directly from Frobenius Theorem and Hermiticity of $\overline{D}$.

The analysis of (3.105) when Q_1, Q_2 are periodic

Most often, the rate of infusion of LAK and IL-2 as defined by the function Q_1 and Q_2 respectively is done by a periodic process of continuous infusions interspaced by recuperative time intervals. We shall give criteria under which the clinically preferred periodic orbit $(0, \Phi_0(t)$ is locally uniformly asymptotically stable. Note that $(0, \Phi_o(t))$ corresponds to the scenario in which cancer cells are extinguished as defined by a2 $[(0, \Phi_0(t) = (0, \widetilde{x}_1(t), \widetilde{w}(t), \widetilde{z}(t))]$.

Theorem 3.30. *Suppose*

(i) $\int_0^\omega [a_{11} - 2a_{12}\widetilde{x}_1(s)]ds < 0$

(ii) $\int_0^\omega [b_{11} - \widetilde{x}_1(s) - b_{22}\,\frac{\widetilde{w}(s)}{1+\widetilde{w}(s)}]ds < 0$

(iii) $\max\{(\eta+1)c_{12}\,\frac{\widetilde{z}(t)}{1+\widetilde{z}(t)} - c_{11}, (1-\eta)\,\frac{c_{12}\widetilde{w}(t)}{(1+\widetilde{z}(t))^2} - d_{11}\} \leq -\alpha,\ \alpha > 0.$

Then the clinically preferred periodic orbit $(0, \Phi_0(t))$ *is uniformly asymptotically stable.*

Proof. The proof follows from the use of the Lozinskii matrix measure and stability, and Floquet theory as explained in Chapter 1 and employed in Theorem 3.25.

□

3.11. Numerical Examples

In this section, we describe some numerical examples to illustrate some of our results. In all examples, the normal cells' growth is described by the logistic equations whereas the tumor cell growth is depicted by the Cox et al. model. The model equations for ACI now assume the form:

$$\begin{cases} \dot{x}_1 = a_{11}x_1 - a_{12}x_1^2 - a_{13}x_1x_2 \\ \dot{x}_2 = \frac{b_{11}x_2}{1+b_{12}x_2} - b_{22}x_2 - b_{23}x_1x_2 - b_{24}\,\frac{x_2w}{1+x_2+w} \\ \dot{w} = c_{01}f_1(t) - c_{11}w + c_{12}\,\frac{wz}{1+z} - c_{13}\,\frac{x_2w}{1+x_2+w} \\ \dot{z} = c_{02}f_2 9t) - d_{11}z - d_{12}\,\frac{wz}{1+z} \\ x_{10} = 1000, \quad x_{20} = 200, \quad w_0 = 0, \quad z_0 = 0. \end{cases}$$

The tumor growth parameters b_{11}, b_{12}, b_{22} are assigned the numerical values extracted from Cox et al. 1980: Comp. Biomed. Res., 13, pp. 437-448. On the otherhand, the normal cell growth parameters a_{11}, a_{12}, a_{13} as well as the other model parameters are assigned values obtained by computer simulations.

In the first two there is a constant infusion LAK and IL2 cells, whereas int he next three examples the infusion is periodic.

Example 3.1. In this example, we set

$$a_{11} = 4.455, \qquad a_{12} = 0.0000250, \qquad a_{13} = 0.00325$$

$$b_{11} = 0.5768, \qquad b_{12} = 0.00008043, \qquad b_{22} = 0.19735$$

$$b_{23} = 0.000075, \qquad b_{24} = 0.000015$$

$$c_{11} = 0.3135, \qquad c_{12} = 0.00225, \qquad c_{13} = 0.455$$

$$d_{11} = 0.2145, \qquad d_{12} = 0.3225$$

$$c_{01} = 100,000 \qquad f_1(t) \equiv 1$$

$$c_{02} = 10,000 \qquad f_2(t) \equiv 1.$$

The computer simulations were performed for $t \in [0, 100]$ days.
The low initial value of $x_{10} = 1000$, assumes that the patient has undergone surgery or radiotherapy prior to the chemotherapy.

This example represents high dose constant infusion ACI therapy. The graph of the numerical solutions for $t \in [0, 100]$, are exhibited in Figure 3.1. A summary of the results is presented as follows:

(i) The cancer cells are annihilated by the time $t \leq 5$ days. If such a model represents chemotherapy of the residual tumor for a cancer bearing patient just after surgical debulking of the tumor, then the outcome of the sequential surgery-chemotherapy treatment is favorable.

(ii) The normal cells x_1 repopulate by proliferating rapidly to the carrying capacity of $K_1 = 180,000$ cells from an initial tumor constrained cell number of $x_{10} = 1000$.

(iii) The pharmacodynamic time profile of the (toxic) IL-2 is such that it is totally washed out of the cancer afflicted organ and possibly the patient's physiological system by $t \leq 20$ days.

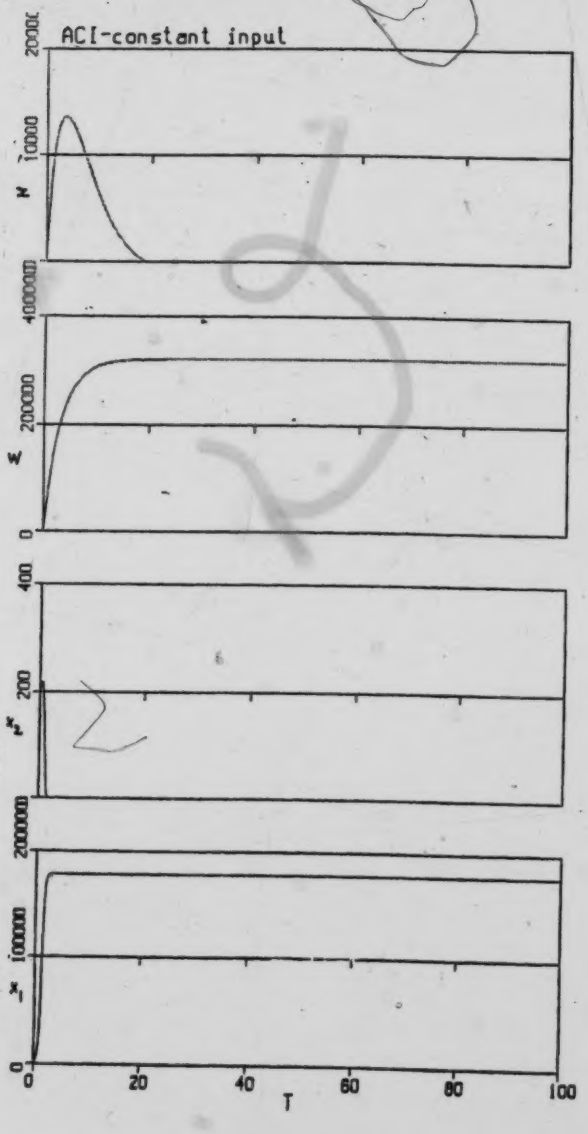


Figure 3.1.

Constant high dose infusion.
Cancer driven extinct.

Example 3.2. In this example, the coefficients are given by the following:

$$a_{11} = 7.00, \qquad a_{12} = 0.0000245, \qquad a_{13} = 0.000741974$$

$$b_{11} = 0.5768, \qquad b_{12} = 0.00008043, \qquad b_{22} = 0.19735$$

$$b_{23} = 0.0000012175, \qquad b_{24} = 0.00000015$$

$$c_{11} = 0.3235, \qquad c_{12} = 0.00225, \qquad c_{13} = 0.455$$

$$d_{11} = 0.1145, \qquad d_{12} = 0.008225$$

$$c_{01} = 100,000, \qquad f_1(t) \equiv 1$$

$$c_{02} = 10,000, \qquad f_2(t) \equiv 1.$$

The computer simulations were performed for $t \in [0, 300]$ days.

This example also depicts a case of high dose constant infusion ACI therapy. The graph of the numerical solutions for $t \in [0, 300]$ are exhibited in Figure 3.2.

A brief summary of the results is as follows:

(i) The normal cells are annihilated within $t \leq 120$ days. This is an example of global asymptotic stability of the rest point $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ which depicts therapeutic failure.

(ii) The cancer cells repopulated by proliferating from $x_{20} = 200$ cells to the lethal carrying capacity of $K_2 = 21,500$ cells within 120 days.

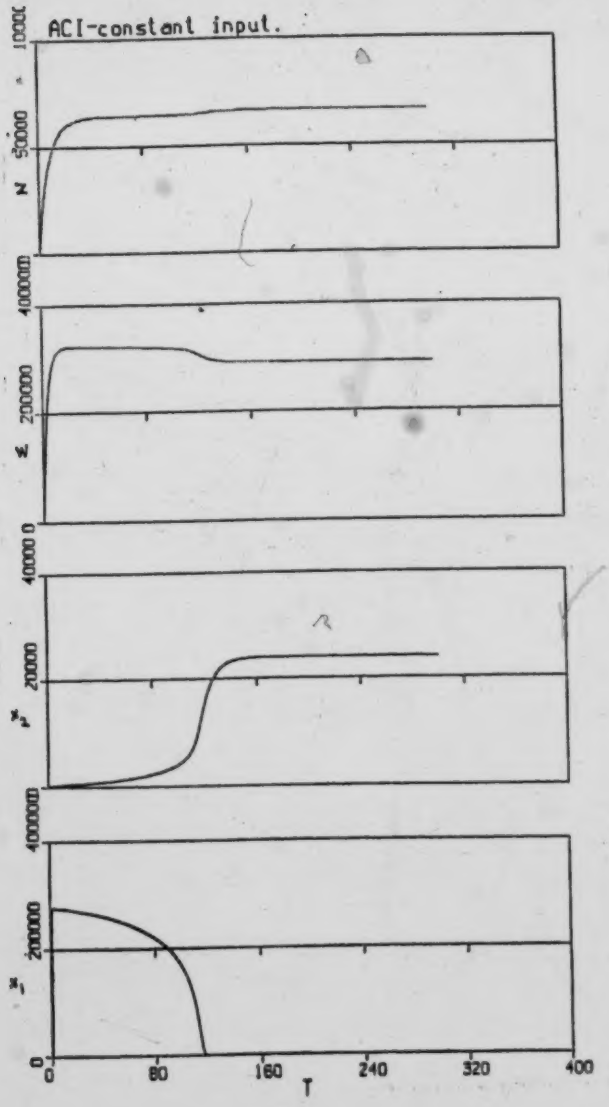


Figure 3.2.

Constant infusion.
Normal cells driven extinct.

Example 3.3. In this example, we assign the following values to the model coefficients:

$$a_{11} = 4.65929, \quad a_{12} = 0.0000152, \quad a_{13} = 0.001394325$$

$$b_{11} = 0.5768, \quad b_{12} = 0.00008043, \quad b_{22} = 0.19735$$

$$b_{23} = 0.00000131305, \quad b_{24} = 0.000018015$$

$$c_{11} = 0.3135, \quad c_{12} = 0.00225, \quad c_{13} = 0.455$$

$$d_{11} = 0.12145, \quad d_{12} = 0.013225$$

$$c_{01} = 1000, \quad c_{02} = 100$$

$$f_1(t) = f_2(t) = f(t) = f(t + 10.5) \text{ i.e. (period = 10.5 days)}$$

σ : (duration of infusion) = 5.5 days

$\Delta\sigma$: (interval between successive infusions) = 5 days.

In particular for *one cycle* of infusions, $f_1(t)$ and $f_2(t)$ have the forms:

$$f_1 = f_2 = f(t) = \begin{cases} 0 & t < 0 \\ 1 & 0 \le t < 5.5 \\ 0 & 5.5 \le t < 10.5. \end{cases}$$

This example depicts the case of *low dose* constant piecewise continuous (or periodic) ACI therapy which is usually the most preferred clinical approach in order to minimize the toxicity of LAK and IL-2.

The graph of the numerical solutions for $t \in [0, 200]$ is presented in Figure 3.3. A brief summary of the simulation results are the following:

(i) The therapy was effective for the time duration $0 \leq t \leq 130$ days. The time set $T_s = [0, 130)$ is called the time domain of therapeutic efficacy of ACI.

(ii) Under the given clinical parametric configuration, the cancer cells eventually drove the normal cells to extinction as a consequence of an oscillatory decrease in the number of LAK cells. This event depicts the scerario in which the clinical oncologist suddenly discovers a lethal repopulation of the tumor in a patient whose cancer has been kept at the subclinical threshold, for almost 4 months.

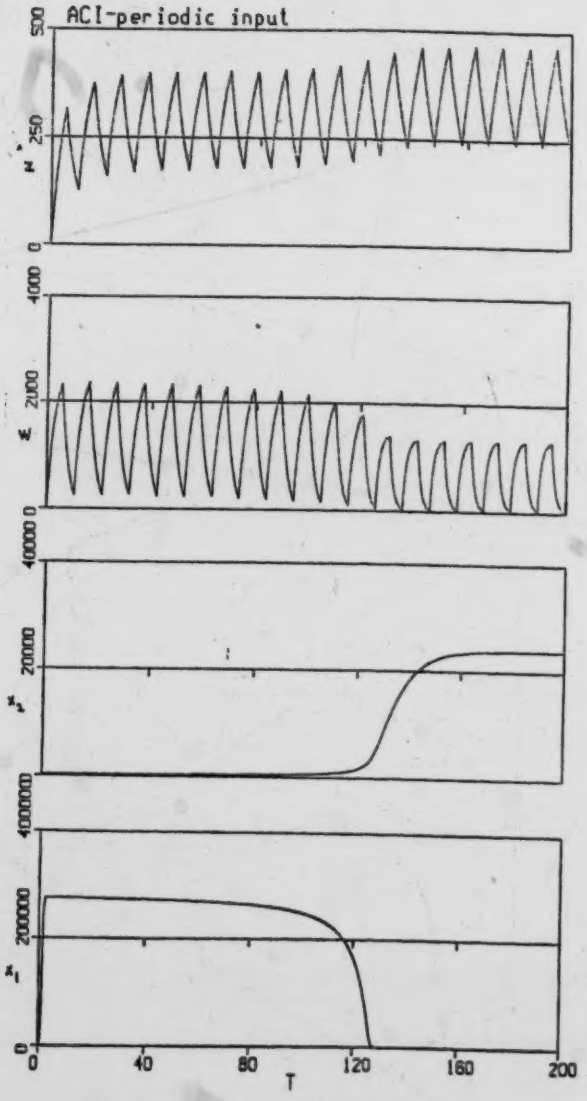


Figure 3.3.

Periodic infusion.
Normal cells driven extinct.

Example 3.4. In this example, the model coefficients are assigned the following values:

$$a_{11} = 3.9455, \quad a_{12} = 0.000027805, \quad a_{13} = 0.001394325$$

$$b_{11} = 0.5768, \quad b_{12} = 0.00008043, \quad b_{22} = 0.19735$$

$$b_{23} = 0.000013975, \quad b_{24} = 0.0015$$

$$c_{11} = 0.3135, \quad c_{12} = 0.00225, \quad c_{13} = 0.455$$

$$d_{11} = 0.12145, \quad d_{12} = 0.013225$$

$$c_{01} = 1000, \quad c_{02} = 100$$

$$f_1(t) = f_2(t) = f(t) = f(t + 10.5).$$

In particular, $f_1, f_2 \quad \sigma, \Delta\sigma$ are as defined in Example 3.

This example depicts the case of low dose periodic (constant piecewise continuous) ACI therapy. The graph of numerical solutions for $t \in [0, 200]$ is displayed in Figure 3.4. The results of the computer simulations are summarized as follows:

(i) The therapy is successful and the cancer cells are annihilated at $t < 5$ days.

(ii) The normal cells in the afflicted organ, repopulate to the carrying capacity of $K_1 = 145,000$ cells.

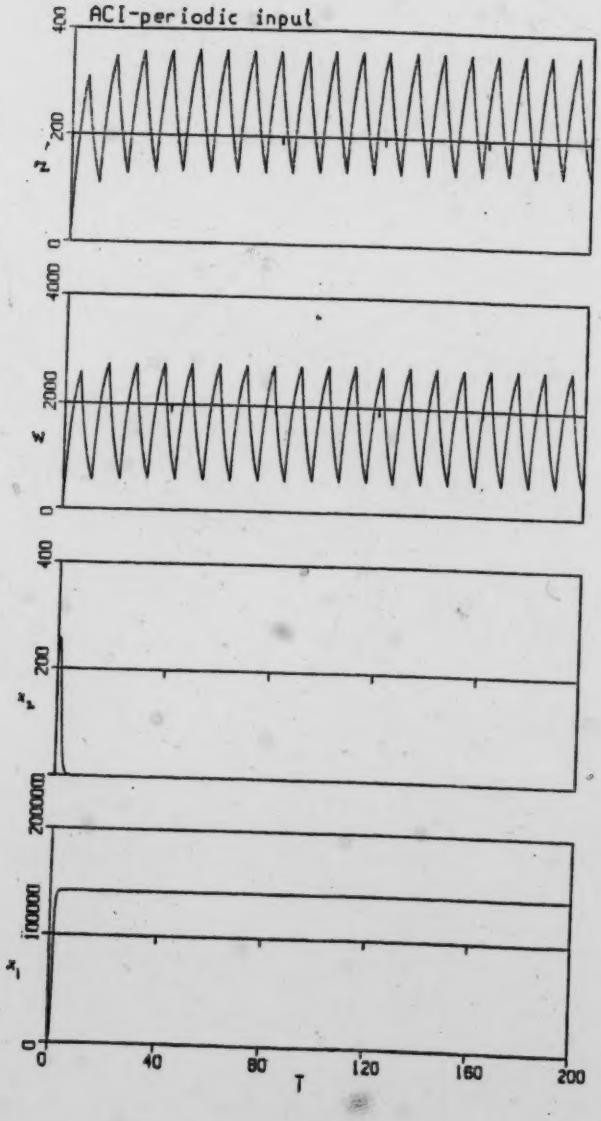


Figure 3.4.

Periodic infusion.
Cancer cells driven extinct.

Example 3.5. In this final example, the model coefficients are assigned the following values:

$$a_{11} = 4.65929, \quad a_{12} = 0.00001520, \quad a_{13} = 0.000139$$

$$b_{11} = 0.5768, \quad b_{12} = 0.00008043, \quad b_{22} = 0.19735,$$

$$b_{23} = 0.0000001243934, \quad b_{24} = 0.00001185,$$

$$c_{11} = 0.3135, \quad c_{12} = 0.00225, \quad c_{13} = 0.455$$

$$d_{11} = 0.12145, \quad d_{12} = 0.013225.$$

The values of $c_{01}, c_{02}, \sigma, \Delta\sigma, f_1(t)$ and $f_2(t)$ are as defined in the previous example.

This example depicts a special case of periodic ACI in which the cancer cells and normal cells co-exist for the therapeutic time duration of $t \in [0, 1000]$ days.

The results of the computer simulations are depicted in Figure 3.5.

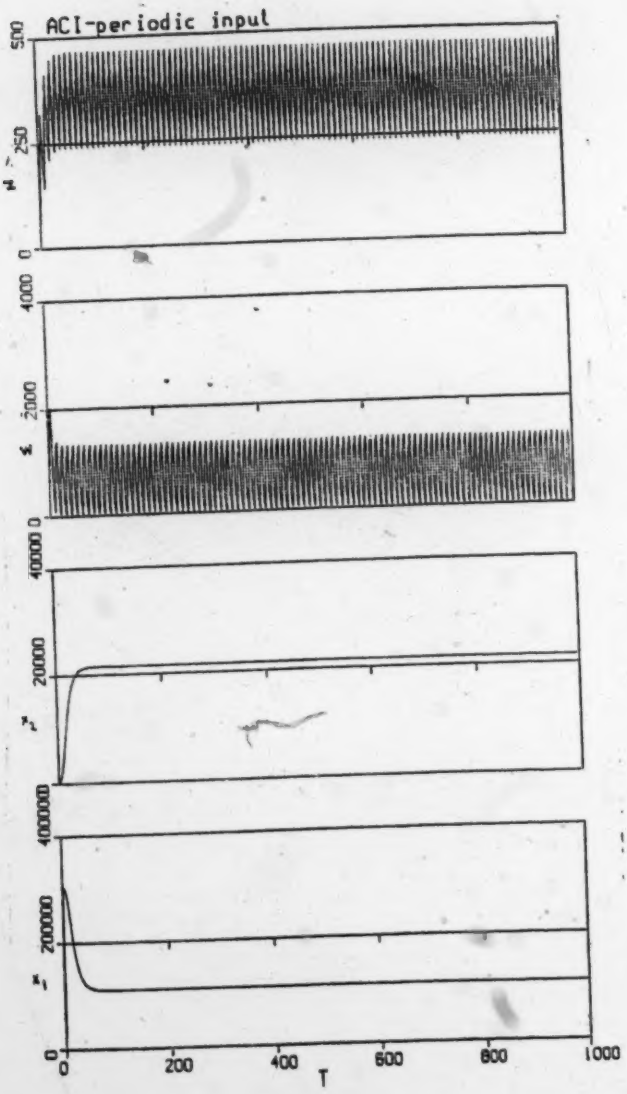


Figure 3.5.

Periodic infusion.
Coexistence of normal and cancer cells.

3.12. Discussion and Conclusions

In the preceeding subsections we used mathematical models to discuss the cancer immunotherapy regimen called Adoptive Cancer (cellular) Immunotherapy (ACI). We employed the mathematical tools of differential analysis, persistence theory, Hopf-Andronov-Poincaré bifurcation, and linear systems theory to give generalized criteria for the therapeutic efficacy of ACI.

When the input functions Q_1 and Q_2 are constant and continuous, we derived criteria for the existence, local stability and global asymptotic stability of the clinically preferred rest point $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$. When $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ does not exist, then the patient has persistent cancer.

We established the circumstances under which $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ exists but is unstable, and also criteria for the existence of a positive interior rest point $E^*[x_1^*, x_2^*, w^*, z^*]$. If the value of x_2^* is below the subclinical threshold of 10^3 cells or for the worst case scenario between 10^3 and 10^9 cells, $E^*[x_1^*, x_2^*, w^*, z^*]$ may persist. But clinically these criteria for the existence of. $E^*[x_1^*, x_2^*, w^*, z^*]$ are too stringent and can hardly be attained in a human cancer patient.

When periodic infusions are used, Theorem 3.25 and later Theorem 3.30 give criteria for local uniform asymptotic stability of the clinically preferred periodic orbit $(0, \Phi_0) = (0, \widetilde{x}_1, \widetilde{w}(t), \widetilde{z}(t))$.

Complications in therapy always occur. Some of these could be explained by the phenomena of chaos and dynamical diseases. In Theorems 3.18 - 3.20, we presented generalized criteria for Hopf bifurcation to occur at $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$

leading to periodic orbits. These ramifications pose complications for the cancer patient and the clinical oncologists. We presented theoretical criteria under which a second bifurcation occurs leading to a family of periodic solutions from the interior equilibrium $E[x_1^*, x_2^*, w^*, z^*]$.

The criteria presented in the preceeding subsections could serve as guidance for the clinical oncologist in such a way that the clinicians could choose their treatment protocols in such a manner to make either $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ or $(0, \Phi_0(t))$ globally asymptotically stable.

3.13. References

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CHAPTER 4
DISCUSSION AND FUTURE RESEARCH

In this final chapter of the thesis we shall present a general review of the results obtained in the previous chapters. Further, we shall discuss the rationale and the method for a combined chemotherapy and immunotherapy model. Future extensions of the model equations to include diffusive aspects of lymphocyte transport and kinetics will also be discussed. Other future research involving optimal control and scheduling of chemotherapy and immunotherapy agents as well as modelling therapeutic complications such as drug resistance in chemotherapy; metastasis and angiogenesis during therapy will be outlined.

4.1. Review of Results

In this section, we shall review the most significant results obtained in the preceeding two chapters.

4.1.1. Review of cancer chemotherapy

In Chapter 2, we have shown that the *single treatment case* is futile and in particular, if $y(t)$ denotes the instantaneous concentration of chemotherapy

agent in the cancer patient, then

$$\lim_{t\to\infty} y(t) = 0, \quad \lim_{t\to\infty} x_2(t) = K_2, \quad \lim_{t\to\infty} x_1(t) = 0. \tag{4.1}$$

Consequently the equilibrium $(0, K_2, 0)$ is a global attractor. Thus the cancer will eventually proliferate to its carrying capacity of K_2 which is of the order of 10^{12} cells, while the normal (healthy) cells in the afflicted organ are annihilated. If a finite sequence of (single) discrete treatments are administered, the therapeutic outcome could be the same unless the intervals between successive drug applications are strategically adjusted to be infinitesimally small or optimally to ensure a sustainable intratumoral concentration. In these adjustments to sustainable blood and intra-tumoral drug concentrations, it will be prudent to use the *continuous treatment case.*

In the continuous treatment case, the anti-cancer drug is administered continuously by intravenous transfusion. The desired disease-free equilibrium,

$\widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1)$ is guaranteed to exist uniquely if

$$\begin{cases} \gamma^{-1}\delta e^{-k\tau} p_1'(0) & < B_1'(0) - D_1'(0) \\ B_1''(x_1) - D_1''(x_1) & < 0 \quad \text{for} \quad 0 \le x_1 \le K_1. \end{cases} \tag{4.2}$$

It will be emphasized that even if (4.2) is violated, it mig oe possible under certain clinical conditions of therapy to ensure the existence $\widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1)$.

It is possible for two values of $\widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1)$ to exist if the following criteria hold:

$$\begin{cases} \gamma^{-1}\delta e^{-k\tau} p_1'(0) & > B_1'(0) - D_1'(0) \\ \max\limits_{0\le x_1\le K_1} [B_1(x_1) - D_1(x_1)] & > \max\limits_{0\le x_1\le K_1} \left[\frac{p_1(x_1)\delta e^{-k\tau}}{\gamma + \eta_1 p_1(x_1)}\right]. \end{cases} \tag{4.3}$$

If two values of $\widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1)$ exist, then a phase space separatrix will demarcate the dynamics in their neighborhoods. It is possible that if (4.3) hold, one of the two values of $\widehat{E}_1(\widehat{x}_1, 0, \widehat{y}_1)$ may be more therapeutically favorable than the other, and that clinical manifestations in the patient will enable the clinician to make the desirable choice.

The instantaneous blood or intra-tumoral concentration of the continuously-transfused anti-cancer drug must be adjusted optimally to prevent the annihilation of all cells including normal cells. We have shown that if

$$\left\{ \begin{array}{ll} & B_1'(0) - D_1'(0) - p_1'(0)u(\overline{y}) < 0 \\ \text{and} & B_2'(0) - D_2'(0) - p_2(0)u(\overline{y}) < 0 \end{array} \right\} \tag{4.4}$$

holds, then the patient will be severely incapacitated, as the anti-cancer drug kills the tumor as well as obliterates all the healthy cells in the afflicted organ.

The criteria for the global asymptotic stability of $\widehat{E}_1[\widehat{x}_1, 0, \widehat{y}]$, the most desired therapeutic outcome, may be very stringent and clinically hard to achieve. We presented alternate criteria for eradication of tumor cells as well as keeping the tumor cell concentration *under* a subclinical threshold. In particular, if

$$\left. \begin{array}{rl} & \overline{\Gamma} - \underline{\Pi}\,\underline{U} < 0 \\ \text{where} & \underline{\sigma}\, y \le u(y) \le \overline{\sigma}\, y \\ & \underline{\sigma}\,\overline{y} \ge M\delta e^{-k\tau} \quad \text{on} \quad [0, \overline{y}], \\ \text{and} & \overline{\Gamma} = \max\limits_{[0,K_2]} \left(B_2'(x_2) - D_2'(x_2)\right) \\ & \underline{\Pi} = \min\limits_{[0,K_2]} P_2'(x_2) \\ & \underline{U} = \frac{m\delta e^{-k\tau}\underline{\sigma}}{[\gamma + \eta_1 p_1(K_1) + \eta_2 p_2(K_2)]\overline{\sigma}}, \quad 0 < m \le f(t) \le M. \end{array} \right\} \tag{4.5}$$

then, the cancer cells (x_2) are eventually annihilated. While these criteria are

less mathematically restrictive the clinical effects of therapy on normal cells (x_1) is not explicitly exhibited.

On the former criteria for global asymptotic stability of $\widehat{E}_1[\widehat{x}_1, 0, \widehat{y}]$ during continuous input chemotherapy, we must state that it may be possible for the clinician to therapeutically manipulate the treatment protocol so as to ensure total eradication of tumor cells while protecting normal cells.

We have demonstrated mathematically that if

$$\left.\begin{array}{l} \overline{\Gamma}_\varepsilon - \underline{\Pi}_\varepsilon \underline{U} < 0 \\ \text{where} \quad \overline{\Gamma}_\varepsilon = \max\limits_{[\varepsilon, K_2]} \left(B_2'(x_2) - D_2'(x_2)\right) \\ \underline{\Pi}_\varepsilon = \min\limits_{[\varepsilon, K_2]} p_2'(x_2). \end{array}\right\} \tag{4.6}$$

Then the cancer cells are kept at a very small concentration which may be well below the subclinical level.

In analysing the model equations for the *no treatment case*, we have shown that the equilibrium $(0, K_2)$ is globally asymptotically stable under the conditions of competitive exclusion. The cancer cells have a higher proliferative potential and by means of aggressive angiogenesis and neo-vascularization, out competes the normal cells to death. In particular, the dynamics of untreated cancer cells is such that

$$\left\{\begin{array}{ll} B_2'(0) - D_2'(0) - D_1 q_2(K_1, 0) & > 0 \\ B_1'(0) - D_1'(0) - K_2 q_1(0, K_2) & < 0. \end{array}\right. \tag{4.7}$$

The criteria (4.7) depict a lack of persistence in $\mathbb{R}^+_{x_1 x_2}$, non-existence of a positive interior equilibrium and the consequent extinction of all normal cells in the afflicted organ.

In order to curtail the toxic consequences of continuous intravenous infusion therapy, it may be clinically advantageous to use optimal, periodic short duration infusions. We presented local criteria for the existence of a periodic solution in $\overline{\mathbb{R}}^{+}_{x_1y}$ space and provided conditions under which this periodic solutions bifurcates into $\overline{\mathbb{R}}^{+}_{x_1x_2y}$. This bifurcation provides a complication of therapy and the clinical oncologist who desires global stability of the periodic orbit $(x_1(t), 0, y(t))$ must avoid such bifurcation by judicious choice of an optimal therapeutic protocol.

4.1.2. Review of cancer immunotherapy

Using the mathematical model (3.0) and associated assumptions, definitions, and hypotheses we presented several criteria for the local asymptotic stability of the clinically desired equilibrium $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$. Such criteria include:

$$\begin{cases} B_1'(x_1) - D_1'(x_1) < 0 \\ B_2'(0) - D_2'(0) - x_1 q_2(x_1, 0) - h_{x_2}(0, w) < 0 \\ \text{Trace } M_{22} < 0 \\ \det M_{22} > 0. \end{cases} \tag{4.7}$$

These are general criteria which must be evaluated for specific tumors with specified B_i, D_i, q_i and h. Specific examples were presented in Chapter 3.

On the other hand, we showed that the equilibrium in which tumor cells obliterate normal cells, i.e. $E_2[0, \widehat{x}_2, \widehat{w}, whz]$ will be unstable if the following criterion

$$B_1'(0) - D_1'(0) = \widehat{x}_2 q_1(0, \widehat{x}_2) > 0 \tag{4.8}$$

holds. The local stability or the global stability of $E_2[0, \widehat{x}_2, \widehat{w}, \widehat{z}]$ depicts the most disastrous outcome of cancer therapy and is least desired.

Usually piece-wise continuous intravenous transfusions are used for administration of LAK cells and IL-2 into the cancer patients. These processes may lead to the existence of periodic levels of LAK and IL-2 in the physiologic system of the patient. The consequences of the periodic fluctuations may complicate the outcome of therapy. We used Floquet Theory to obtain the criteria under which the desired periodic solution $(0, \Phi_0)$ will be locally asymptotically stable. Using the Lozinski Matrix Measure, it was possible to obtain alternate criteria for local asymptotic stability of $(0, \Phi_0)$. Such criteria are given by (4.9).

$$\begin{aligned} \max\{p_{11}\} &< 0 \\ \max\{p_{22} + |p_{12}| + |p_{32}|\} &< 0 \\ \max\{p_{33} + |p_{43}|\} &< 0 \\ \max\{p_{44} + |p_{34}|\} &< 0 \end{aligned} \tag{4.9}$$

where

$$p_{11} = B_1'(x_1(t)) - D_1'(x_1(t))$$

$$p_{22} = B_2'(0) - D_2'(0) - x_1(t)q_2(x_1(t), 0) - h_{x_2}(0, w(t))$$

$$P_{12} = -x(t)q_1(x_1(t), 0)$$

$$p_{32} = -\beta h_{x_2}(0, w(t))$$

$$p_{33} = f_w(w(t), z(t)) - \alpha_1 e_1'(w(t)) - \beta h_w(0, w(t))$$

$$p_{34} = f_z(w(t), z(t))$$

$$p_{43} = -\eta f_w(w(t), z(t))$$

$$p_{44} = -e_2'(z(t)) - \eta f_z(w(t)) \tag{4.10}$$

with all other $p_{ij} \equiv 0.$ (4.11)

Criteria (4.9) must be evaluated for any given tumor and drug protocol.

The criteria presented for global asymptotic stability of $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ are very stringent and the clinical oncologist by prudent choice of therapy conditions may manipulate the constants associated with the Liapunov functions in such a way as to ensure total annihilation of all cancer cells. This may not be always feasible for certain cancers at advanced stages of growth or within certain locations in the human anatomy.

We also stated conditions under which Hopf-Andronov-Poincaré bifurcations occur at the clinically desired equilibrium $E_1[\overline{x}_1, 0, \overline{w}, \overline{z}]$ leading to undesired complications of therapy. We have shown that this occurs when the following criteria hold for a bifurcation parameter $\mu = \nu_1$:

$$\begin{cases} \frac{d}{d\mu}[f_w(w, z; \mu) - \eta f_z(w, z; \mu)] > 0 & (4.12) \\ \left.\begin{array}{c} B_1'(\overline{x}_1) - D_1'(\overline{x}_1) < 0 \\ B_2'(0) - D_2'(0) - \overline{x}_1 q_2(\overline{x}_1, 0) < 0 \end{array}\right\} & (4.13) \\ \text{Trace } \overline{A}_{22} = 0 \quad \text{with} \quad \det \overline{A}_{22} > 0. & (4.14) \end{cases}$$

4.2. A Mathematical Model for Chemo-Immunotherapy

In this section we shall give a preview of a proposed future project presenting a combined model for cancer chemotherapy and immunotherapy. The motivation for this approach comes from clinical research. Goldfarb et al. [7] have demonstrated that chemo-immunotherapy with NK-LAK cells and IL-2 plus anti-cancer drugs may be more effective then adoptive immunotherapy *alone*. They provided clinical evidence to the fact that chemo-immunotherapy is able to eradicate disseminated micro-metastasis of the tumor. They solved the problem of compounded drug toxicity by covalently conjugating the chemotherapy agent Doxorubicin to the IL-2 activated NK-LAK cells using a membrane-binding lipophilic dye called Zyn-Linkers, [7]. Since NK-LAK cells selectively accumulate within tumor metastasis, this process does not lead to systemic distribution and dissipation of the chemotherapy agent except within the cancerous metastasis. Thus the chemotherapy induced killing of normal cells is minimal. The proposed model equations take the form:

$$
\begin{aligned}
\dot{x}_1 &= B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)u(y) \\
\dot{x}_2 &= B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - p_2(x_2)u(y) - h(x_2, w) \\
\dot{y} &= \begin{cases} 0 & t < \tau \\ \delta_0 f(t-\tau)e^{-k\tau} - [\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2)]u(y) & \tau \le t < \tau + \sigma \\ -[\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2)]u(y) & t \ge \tau + \sigma \end{cases} \\
\dot{w} &= Q_1 + f(w, z) - \beta h(x_2, w) - \alpha_1 e_1(w) \\
\dot{z} &= Q_2 - \eta f(w, z) - \alpha_2 e_2(z) \qquad (4.15) \\
x_1(t_0) &= x_{10} \ge 0, \qquad w(t_0) = w_0 \ge 0
\end{aligned}
$$

$$x_2(t_0) = x_{20} \geq 0, \qquad z(t_0) = z_0 \geq 0$$

$$y(t_0) = y_0 \geq 0.$$

The functions $B_i, D_i, Q_i, P_i, h, e_i, f,$ are as defined in preceeding chapters.

The possible equilibria are of the form

$$E_0^c = [0, 0, \mathring{y}, \mathring{w}, \mathring{z}],$$

$$E_1^c = [\widehat{x}_1, 0, \widehat{y}, \widehat{w}, \widehat{z}]$$

$$E_2^c = [0, \overline{x}_2, \overline{y}, \overline{w}, \overline{z}]$$

$$E_3^c = [x_1^*, x_2^*, w^*, z^*].$$

The local linearized stability of the model equations (4.15) in a neighborhood of the equilibria $E_i^c, \quad i = 0, 1, 2, 3$ would be analyzed using the techniques exhibited in the thesis.

We propose to investigate the existence of periodic orbits and limit cycles under clinically plausible parametric configurations. Numerical analyses of the results and computer simulations will be performed to illustrate the practical dynamics of such a combined model.

We hope to obtain criteria for Hopf bifurcations and possibly Crandal-Rabinowitz [5] bifurcations form eigenvalues of the system equations. We would also hope to give estimates on the existence region for small-parameter periodic solutions of the system equations as described by Freedman [6].

4.3. Other Future Research Projects

In this subsection we shall discuss some research projects which we propose to undertake in the future.

4.3.1. Diffusion models for chemotherapy and immunotherapy

In Adoptive Cancer Immunotherapy (ACI) there is some suggestion that the inclusion of diffusion terms in the model equations is appropriate [8,9]. We will be interested in mathematical modelling such a system and carrying out linearized stability and bifurcation analysis. Similar considerations also hold for chemotherapy in which it may be appropriate to include a diffusion term for drug transport into the tumor. The model equations for chemotherapy and immunotherapy may take the following forms: Let Ω be an open set in $\mathbb{R}^3$ with boundary $\partial\Omega$. The outward normal derivative on $\partial\Omega$ is denoted by $\frac{\partial}{\partial n}$. We shall denote the Laplacian operator by Δ, where

$$\Delta = \frac{\partial^2}{\partial X_1^2} + \frac{\partial^2}{\partial X_2^2} + \frac{\partial^2}{\partial X_3^2} \tag{4.16}$$

$$X = (X_1, X_2, X_3) \in \mathbb{R}^3.$$

Let d_i, $i = 1, 2$, where $d_i > 0$ for all i, denote the diffusion coefficients.

Then the reaction-diffusion type model equations for ACI is depicted by the following system:

$$\frac{\partial x_1}{\partial t} = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2)$$

$$\frac{\partial x_2}{\partial t} = B_2(x_2) - D_2(x_2) - x_2 x_1 q_2(x_1, x_2) - h(x_2, w)$$

$$\frac{\partial w}{\partial t} = d_1 \Delta w + Q_1 + f(w, z) - \beta h(x_2, w) - \alpha_1 e_1(w)$$

$$\frac{\partial z}{\partial t} = d_2 \Delta z + Q_2 - \eta f(w, z) - \alpha_2 e_2(z). \tag{4.17}$$

The initial conditions are given by

$$\left.\begin{aligned} x_1(X,0) = x_{10}(X), \qquad & x_2(X,0) = x_{20}(X) \\ w(X,0) = w_0(X), \qquad & z(X,0) = z_0(X) \\ X = (X_1, X_2, X_3) \in \Omega. & \end{aligned}\right\} \tag{4.18}$$

The Dirichlet boundary conditions

$$(x_1, x_2, w, z) = (r_{10}, r_{20}, r_{30}, r_{40}) \quad \text{on} \quad \partial\Omega \times \mathbb{R}_+ , \tag{4.19}$$

or the Neumann boundary conditions

$$\left(\frac{\partial x_1}{\partial n}, \frac{\partial x_2}{\partial n}, \frac{\partial w}{\partial n}, \frac{\partial z}{\partial n}\right) = (x_{10}, s_{20}, s_{30}, s_{40}) \quad \text{on} \quad \partial\Omega \times \mathbb{R}_+ , \tag{4.20}$$

will be used. The choices for r_{i0}, s_{i0}, $i = 1, 2, 3, 4$ will be such as to reflect on the nature physiological processes involved.

The goals of the research project will include the following:

$R(i)$ Obtain conditions for local and global existence of solutions to (4.17) in a suitably chosen Banach space.

$R(ii)$ Study the effect of metastasis on therapy. In this regard, the choices of r_{i0} and s_{i0}, $i = 1, 2, 3, 4$ such that $r_{i0} > 0$ and $s_{i0} = (0, s_{20}, s_{30}, s_{40})$ with

$s_{20} > 0, \quad s_{30} \geq 0, \quad s_{40} \geq 0$ may be considered.

$R(iii)$ Determine criteria for boundedness, and invariance of system (4.17).

$R(iv)$ To investigate the existence and nature of eigenvalues and periodic solutions using theorems on linearized stability for partial differential equations and Green's functions and boundary value theory for each of the stated boundary conditions.

The reaction-diffusion equations for continuous infusion cancer chemotherapy is formulated along similar arguments and take the form:

$$\begin{aligned}
\frac{\partial x_1}{\partial t} &= B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)u(y) \\
\frac{\partial x_2}{\partial t} &= B_2(x_2) - D_2(x_2) - x_2 x_1 q_2(x_1, x_2) - p_2(x_2)u(y) \\
\frac{\partial y}{\partial t} &= \begin{cases} 0 & t < \tau \\ D_1 \Delta y + \delta_0 f(t-\tau)e^{-k\tau} - [\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2)]u(y) & \\ & \tau \leq t < \tau + \sigma \end{cases}
\end{aligned} \tag{4.21}$$

where $D_1 > 0$ is the diffusion constant.

The Dirichlet boundary conditions are

$$(x_1, x_2, y) = (p_{10}, p_{20}, p_{30}) \quad \text{on} \quad \partial\Omega \times \mathbb{R}_+ \tag{4.22}$$

and the Neumann boundary conditions are

$$\left(\frac{\partial x_1}{\partial n}, \frac{\partial x_2}{\partial n}, \frac{\partial w}{\partial n}, \frac{\partial z}{\partial n}\right) = (k_{10}, k_{20}, k_{30}) \quad \text{on} \quad \partial\Omega \times IR_+ . \tag{4.23}$$

Metastatic spread of cancer can be investigated by the choice $k_{0i} = (0, k_{20}, k_{30})$ where $k_{20} > 0$, $k_{30} \geq 0$. The research goals are as depicted by $R(i - iv)$.

4.3.2. Mathematical modeling of drug resistance

The therapeutic failure of an anti-cancer agent may be attributed to several reasons including the following:

$F(i)$ The heterogeneity and consequent differential sensitivities of the heterogeneous cancer subpopulations are such that the drug destroys only the drug-sensitive cancer cells leaving the non-drug-sensitive cancer cells to repopulate the tumor.

$F(ii)$ The anti-cancer drug is degraded metabolically at such a rate that the optimal concentration in the tumor is not attained. This process may be mediated by enzymes. Another possibility is enzyme mediated decrease in diffusion of drugs into the tumor cells.

$F(iii)$ Non-optimal drug administration in which the time interval between successive continuous drug infusions are not prudently chosen such that the tumor cells have sufficient time to recuperate and repopulate the tumor.

$F(iv)$ Aggressive proliferation, angiogenesis and neo-vascularization of the tumor enables cancer cells to survive therapy. In this case, drugs such as Angiostatin which impedes neo-vascularization may be effective. Another scenario will be the possibility of the tumor carrying capacity K_2 being monotonic

or oscillating with time.

In the future we propose to formulate and investigate mathematical models depicting most or all of the aspects described by $F(i-iv)$. Let $r(t)$ denote the instantaneous concentration of drug-induced therapy resistant cancer cells. Then a prototype mathematical model for drug resistance is given by the following system of ordinary differential equations:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1x_2q_{12}(x_1,x_2) - x_1rq_{1r}(x_1,r) - p_1(x_1)u(y)$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_1x_2q_{21}(x_1,x_2) - x_2rq_{2r}(x_2,r) - p_2(x_2)u(y)$$
$$- p_3(x_2)(u(y)$$

$$\dot{r} = kp_3(x_2)u(y) - x_1rq_{r_1}(x_1,r) - x_2rq_{r_2}(x_2,r)$$

$$\dot{y} = \begin{cases} 0 & t < \tau \\ \delta_0 e^{-k\tau} f(t_\tau) - (\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2) & \\ \qquad + \nu_3 p_3(x_2))u(y), & \tau \le t < \tau + \sigma \\ -(\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2))u(y), & t \ge \tau + \sigma \end{cases}$$

$$x_1(t_0) = x_{10} \ge 0, \quad x_2(t_0) = x_2 \ge 0, \quad r(t_0) = r_0 = 0$$

$$y(t_0) = y_0 = 0. \tag{4.24}$$

(γ is the drug degradation constant, k is the drug resistant cancer cell proliferation constant).

In the prototype model (4.24), the term $p_3(x_2)u(y)$ depicts the rate at which the drug resistance sub-population of cancer cells is generated.

We shall investigate the following scenarios associated with drug resistance.

$$\frac{\partial x_2}{\partial t} = B_2(x_2) - D_2(x_2) - x_2 x_1 q_2(x_1, x_2) - h(x_2, w)$$

$$\frac{\partial w}{\partial t} = d_1 \Delta w + Q_1 + f(w, z) - \beta h(x_2, w) - \alpha_1 e_1(w)$$

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will be used. The choices for r_{i0}, s_{i0}, $i = 1, 2, 3, 4$ will be such as to reflect on the nature physiological processes involved.

The goals of the research project will include the following:

$R(i)$ Obtain conditions for local and global existence of solutions to (4.17) in a suitably chosen Banach space.

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$s_{20} > 0, \quad s_{30} \geq 0, \quad s_{40} \geq 0$ may be considered.

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where $D_1 > 0$ is the diffusion constant.

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$F(iii)$ Non-optimal drug administration in which the time interval between successive continuous drug infusions are not prudently chosen such that the tumor cells have sufficient time to recuperate and repopulate the tumor.

$F(iv)$ Aggressive proliferation, angiogenesis and neo-vascularization of the tumor enables cancer cells to survive therapy. In this case, drugs such as Angiostatin which impedes neo-vascularization may be effective. Another scenario will be the possibility of the tumor carrying capacity K_2 being monotonic

or oscillating with time.

In the future we propose to formulate and investigate mathematical models depicting most or all of the aspects described by $F(i-iv)$. Let $r(t)$ denote the instantaneous concentration of drug-induced therapy resistant cancer cells. Then a prototype mathematical model for drug resistance is given by the following system of ordinary differential equations:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1x_2q_{12}(x_1,x_2) - x_1rq_{1r}(x_1,r) - p_1(x_1)u(y)$$

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$$- p_3(x_2)(u(y)$$

$$\dot{r} = kp_3(x_2)u(y) - x_1rq_{r_1}(x_1,r) - x_2rq_{r_2}(x_2,r)$$

$$\dot{y} = \begin{cases} 0 & t < \tau \\ \delta_0 e^{-k\tau} f(t_\tau) - (\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2) & \\ \qquad + \nu_3 p_3(x_2))u(y), & \tau \le t < \tau + \sigma \\ -(\gamma + \nu_1 p_1(x_1) + \nu_2 p_2(x_2))u(y), & t \ge \tau + \sigma \end{cases}$$

$$x_1(t_0) = x_{10} \ge 0, \quad x_2(t_0) = x_2 \ge 0, \quad r(t_0) = r_0 = 0$$

$$y(t_0) = y_0 = 0. \tag{4.24}$$

(γ is the drug degradation constant, k is the drug resistant cancer cell proliferation constant).

In the prototype model (4.24), the term $p_3(x_2)u(y)$ depicts the rate at which the drug resistance sub-population of cancer cells is generated.

We shall investigate the following scenarios associated with drug resistance.

(i) τ outcompetes both x_1 and x_2.

(ii) $\gamma \geq \max_{\tau \leq t < \infty} [\delta_0 e^{-k\tau} f(t-\tau)]$

(iii) $B_2(x_2) - D_2(x_2) \equiv x_2 g_2(x_2, K(t))$ where

a. $g_2(x_2, K_2(t)) \in C^1[\mathbb{R}_+ \times \mathbb{R}_+, \mathbb{R}]$

b. $0 < \underline{k}_2 \leq K_2(t) \leq \overline{K}_2 < \infty, \quad t \in \mathbb{R}_+$

c. $g_2(0, K_2(t)) > 0, \quad \frac{\partial g_2}{\partial x_2} < 0, \quad \frac{\partial g_2}{\partial K_2} > 0, \quad g_2(K_2(t), K_2(t)) = 0$

d. $\dot{K}_2(t) \neq 0$ eventually as $t \to \infty$.

d*. $\liminf_{t \to \infty} K_2(t) = \underline{k}_2, \quad \limsup_{t \to \infty} K_2(t) = \overline{K}_2.$

4.3.3. Optimal control of cancer chemotherapy

The importance of the choice of optimal drug administration protocol in cancer chemotherapy have been emphasized and investigated by several authors including Bellman et al. [2], Murray [10], Swan [11], Coldman and Boldrini [4].

We will investigate and try to find optimal control policies for the cancer chemotherapy models presented in the preceeding chapters. Some previous investigators chose drug kinetics which may not describe all the features associated with cancer chemotherapy. These simplified choices compromise the applicability of the mathematical derived optimal policies to real life problems associated with cancer.

We shall try to choose model functions and parametric configurations which

are close to clinical reality. Some of the optimal control problems we shall attempt to solve, include the following.

Problem 1.

Let:

i. $L(v)$ denote the specific drug concentration in cancer cells and normal (healthy) cells,

ii. $U(t)$ denote the *control*, i.e. the rate at which (low dose) anti-cancer drug is piece-wise continuously transfused into the cancer patient,

iii. $[0, T]$ be the treatment interval,

iv. $n_{20} = 10^3$ be the subclinical cancer cells' number,

v. n_{10} be the threshold normal cell number required for survival and regeneration of the anatomic organ of the body in which the cancer cells are localized.

Consider the model equations:

$$\dot{x}_1 = B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)L(v)$$

$$\dot{x}_2 = B_2(x_2) - D_2(x_2) - x_2 x_1 q_2(x_1, x_2) - p_2(x_2)L(v)$$

$$\dot{v} = \delta_0 e^{-k\tau} U(t) - (\gamma + \eta_1 p_1(x_1) + \eta_2 p_2(x_2))L(v)$$

$$x_1(t_0) = x_{10}, \quad x_2(t_0) = x_{20}, \quad v(t_0) = v_0. \tag{4.25}$$

Then the optimal control problem 1.A is defined as follows:

$$\text{minimize} \quad J_1 = -\int_0^T [B_1(x_1) - D_1(x_1) - x_1 x_2 q_1(x_1, x_2) - p_1(x_1)L(v)]^2 dt$$

and

$$\text{maximize} \quad J_2 = \int_0^T [B_2(x_2) - D_2(x_2) - x_1 x_2 q_2(x_1, x_2) - p_2(x_2)L(v)^2 dt$$

subject to (4.25) and the following constraints:

$$\begin{aligned} n_{10} \le x_1(t) \le K_1 \\ 0 \le x_2(t) \le n_{20} \end{aligned} \tag{4.26}$$

where $U(t) \in [0, u_m] \forall t \in [0, T]$

$$u_m = \max_{[0,T]} U(t).$$

In order to ensure that the control lies in the specified time domain, we shall investigate a refinement of problem 1A as defined in problem 1B:

Let $T, \widetilde{T}$ be fixed with $T < \widetilde{T}$. Define the function $h(t)$:

$$h(t) = \begin{cases} 1 & \text{if} \quad 0 \le t \le T \\ 0 & \text{if} \quad T < t \le \widetilde{T}. \end{cases} \tag{4.27}$$

Minimize $J_1 = -\int_0^{\widetilde{T}} h(t)[B_1(x_1) - D_1(x_1) - x_1x_2q_1(x_1,x_2) - p_1(x_1)L(v)]^2dt$

and

minimize $J_2 = \int_0^{\widetilde{T}} h(t)[B_2(x_2) - D_2(x_2) - x_1x_2q_2(x_1,x_2) - p_2(x_2)L(v)]^2dt$

subject to:

$$n_{10} \leq x_1(t) \leq K_1$$

$$0 \leq x_2(t) \leq n_{20}$$

$$U(t) \in [0, u_m], \quad \forall t \in [0, \widetilde{T}].$$

□

Remark. The optimal control problems described in 1A and 1B are multi criterion optimization problems. It may be noted that minimization of one performance criterion may alter or affect the other criterion in a contradictory way; and there may not exist a unique optimal control. One way of resolving this impasse is to use the Pareto version of Pontryagin's Maximum Principle as established by Yu and Leitmann [12]. This technique have been applied by several authors including Murray [10], Swan [11] and Costa and Boldrini [4].

We then formulate problem 1C as follows:

For each pair of real numbers (p, q) satisfying $0 \leq p, \quad q \leq 1$ and $p+q = 1$,

define,

$$J_{pq} = {}_pJ_2 + {}_qJ_1$$

$BV[0,t_f]$.: Class of bounded variation functions defined on $[0,t_f]$.

$$A(t_f): \begin{cases} u \in BV[0,t_f], \quad 0 \le U(t) \le u_m \\ \forall\, t \in [0,t_f]. \end{cases}$$

Find a time $0 \le t_f^* < +\infty$ and a $BV[0,t_f^*]$ function,

$$U : [0,t_f^*] \to IR$$

such that $0 \le U^*(t) \le u_m$ and in such a way that it will be the optimal drug concentration in the sense that

$$J_{pq}(u^*(\cdot), t_f^*) = \min \{J_{pq}(u,t_f),\ U \in A(t_f),\ \forall\, t_f > 0\}$$

where J_1 and J_2 are as defined respectively in problems 1A and 1B.

This optimal control problem may be solved for several possibilities such as:

(i) $p = 1, \quad q = 0$

(ii) $p = 0, \quad q = 1$

(iii) $0 < p, \quad q > 1, \quad p + q = 1.$

□

Remark 4.1. It may be possible that some of the optimal control problems de-

scribed may lead to criteria which will be difficult to implement by the clinical oncologist. We shall also investigate the possibility of using the techniques of Dynamic Programming and Bellman's Optimally Criteria on Sequential Optimalization, cf. [1]. Similar problems will be investigated for cancer immunotherapy.

□

4.4. References

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